Surgical Reconstructive Therapy for the Management of Peri-implantitis: An AAP/AO Systematic Review and Network Meta-analysis

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Purpose: Reports on the occurrence of peri-implant diseases date back nearly two decades. Despite the attempts taken toward the management of this disease, the literature still lacks a common remedy for predictable treatment. This best evidence consensus review was conducted in preparation for the joint consensus between the American Academy of Periodontology (AAP) and the Academy of Osseointegration (AO) to systematically analyze the clinical research in the field of surgical reconstructive therapy for peri-implantitis. ***Materials and Methods:*** A detailed systematic search was conducted to identify eligible clinical research reporting the outcomes of surgical reconstructive therapy for peri-implantitis. The retrieved nonrandomized studies were analyzed descriptively, while the data from randomized control trials (RCTs) were fit to a series of mixed models that analyzed the individual components of the study arms and rendered treatments for the outcomes of probing pocket depth (PPD) reduction, radiographic marginal bone level (Rx MBL) gain, reduction in bleeding on probing (BoP) and suppuration (SUP), as well as mucosal recession (MREC). ***Results:*** A total of 18 reports on RCTs were eligible for quantitative assessment (635 patients, 687 implants). The results indicated that surgical reconstructive approaches for peri-implantitis (based on 319 patients and 345 implants), when compared to a nonreconstructive treatment modality (ie, open flap debridement alone based on 316 patients and 342 implants), was effective in reducing PPD, minimizing MREC, as well as increasing Rx MBL gain. However, there was no additional benefit from employing a reconstructive approach regarding the outcomes of BoP and SUP reduction. Several other baseline covariates such as site (initial PPD, MBL, and BoP) and systemic factors (eg, smoking) were also found to significantly impact the therapeutic outcomes. Mechanical decontamination methods as well as individual components of the augmentation approach were also found to significantly affect the outcomes. ***Conclusions:*** Within the limitations of this study, it was demonstrated that the surgical treatment of infrabony peri-implantitis defects can lead to PPD reduction, MREC reduction, and Rx MBL gain and was found to be superior to nonreconstructive treatment. However, there were no significant differences between the two modalities of therapy for the outcomes of BoP and SUP. Reconstructive therapy may provide a suitable approach for managing peri-implantitis–related infrabony defects. *Int J Oral Maxillofac Implants 2025;40(suppl):s1–s48. doi: 10.11607/jomi.2025suppl1*

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Dental implant complications are among the greatest challenges faced in dentistry today due to the widespread use of dental implants in general and specialty practices.[1–3] The biologic complication of peri-implantitis likely ranks as the most prevalent and poses one of the greatest threats to success across different disciplines of dentistry today.[4]

Despite nearly two decades of research on managing this infectious and inflammatory disease along with the plethora of data generated through clinical research, there is still a lack of consensus on which treatment modalities can reliably produce predictable positive outcomes. Initially, nonsurgical therapies were evaluated, borrowing from the principles of periodontology where scaling and root planing of natural dentition is the very first step. However, these interventions alone yielded minimal and inadequate results, particularly for more advanced forms of the disease.[5–9]

Surgical therapies—such as open flap debridement and resective approaches—were proposed and evaluated, providing greater access to the peri-implant defect and enhancing debridement and detoxification.[3] Nonetheless, these approaches were also documented with varying levels of success[10–12] and, importantly, with significant recurrence rates.[13]

Surgical reconstructive therapies have also been employed, aiming not only at disease resolution and reduction of probing depth but also at reconstructing the lost peri-implant supporting bony structure[14–18] in hopes of increasing long-term maintenance and predictability. In this effort, researchers and clinicians adopted many principles of guided bone regeneration, including various regenerative approaches, biomaterials (ie, different bone grafts and barrier membranes), as well as bioactive agents.[14,15,19] Still, conflicting evidence exists from individual studies, and conclusions from previous systematic reviews seem inconclusive. One could assume that the reason for this might be due to the number of variables present at any implant site, all of which could contribute to the presence of the disease and/or its lack of resolution, thus limiting the regenerative response.

Therefore, in preparation for the joint consensus between the American Academy of Periodontology and the Academy of Osseointegration, the current best evidence consensus review was constructed to systematically underline and statistically analyze the research on this topic, with the following focus questions in mind:

- What are the currently used surgical reconstructive approaches for the treatment of peri-implantitis, and how effective are these approaches compared to a nonreconstructive modality (ie, open flap debridement alone) in terms of the most relevant clinical outcomes?
- How do different surgical and regenerative components of the rendered therapies influence clinical outcomes?
- What other factors can influence the outcomes of disease management and reconstructive surgical treatment of peri-implantitis?

MATERIALS AND METHODS

Protocol Registration and Reporting Format

To ensure transparency and reduce bias, the protocol of this study was registered prior to initiation in the PROSPERO database[20] (ID No.: CRD42023479738). The manuscript was also prepared following the Cochrane Collaboration guidelines[21] and was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analysis Extension (PRISMA) statement for systematic reviews incorporating network meta-analyses for health care interventions.[22,23] It was planned that if at any time after protocol registration an amendment to the original submission was performed, it would be conveyed on the electronic database with its corresponding time stamp.

Objectives

The goal of this systematic review was to address the previously stated focus questions concerning surgical reconstructive therapy for peri-implantitis.

Population, Intervention, Comparison, Outcome, Study Design (PICOS)

The following PICOS framework was used to guide the electronic and manual search of the literature toward assessing the focus questions of the current study:

- **P** *(population):* Patients (human adults) presenting with at least one dental implant previously in function (restored and in function for at least 1 year) with peri-implantitis that was either diagnosed and specified according to the case definition by the American Academy of Periodontology/European Federation of Periodontology 2017 World Workshop[24–29] or diagnosed based on clinical and radiographic parameters.
- **I** *(intervention):* Any reconstructive treatment for peri-implant bone defects as a result of a clinical diagnosis of peri-implantitis, in which bone grafting through the use of bone substitutes or bone replacement grafts (with or without the use of barrier membranes) were used. The aim of the conducted procedure must have been to reconstruct the peri-implant bone and eliminate the local disease, establishing peri-implant health. The use of biologic agents and/or biologic mediators was allowed, as well as the inclusion of combination therapies.
- **C** *(comparison):* All suitable comparisons among the included interventions and studies were explored, including control groups such as nonreconstructive surgical therapy for peri-implantitis (ie, the employment of open flap debridement to serve as a positive control). Resective approaches were not considered due to differences in the original treatment and recruitment criteria (eg, a horizontal and/or nonregenerative bony architecture, which would significantly confound the analysis and any relative assessment). Different reconstructive remedies or combination grafts were also considered, as well different healing protocols with regard to the management of prosthetic suprastructures (eg, a submerged or a nonsubmerged regenerative healing approach).

- **O** *(outcomes):* Studies must have provided at least one of the following outcomes after the rendered treatment:
    - Success of treatment (definition must be clearly stated or referred to in the published report) or resolution of disease (typically provided in percentage or other reported measures)
    - Bleeding on probing ([BoP]: exact assessment should be reported in the published report)
    - Suppuration (SUP)
    - Mucosal indices to convey presentation of local clinical mucosal inflammation
    - Probing pocket depth (PPD)
    - Change in mucosal levels, defined as mucosal recession (MREC)
    - Radiographic (Rx) assessment of bone level changes, marginal bone levels (MBL), and other similar outcomes
    - Implant survival as a binary measure
    - The presentation of any adverse events
    - Any patient-level outcome such as intraoperative discomfort or pain, postoperative discomfort or pain, patient satisfaction, effect on quality of life, and treatment time
- **S** *(study design):*
    - Prospectively conducted and controlled interventional human studies (whether split-mouth or parallel design) with at least a 12-month postoperative follow-up (after the final intervention), a minimum of 10 patients per treatment arm, and published in a peer-reviewed journal (such as prospectively conducted nonrandomized trials, prospectively conducted case series with a proper protocol, etc) were considered.
    - For a quantitative assessment of therapeutic protocols and treatment effects (ie, a meta-analysis or a relative efficacy assessment of the therapies), only data from prospectively conducted randomized controlled clinical trials (RCTs) with a defined protocol were used.

Eligibility Criteria

The inclusion criterial were as follows: *(1)* Prospectively conducted human research on surgical reconstructive or surgical nonreconstructive therapy for peri-implantitis, and *(2)* articles with at least one of the abovementioned outcomes, interventions, and study design. Note that no language, geographic location, or source restrictions were included.

The exclusion criteria were as follows: *(1)* studies that focused on or had conducted a resective approach (via a statement of any bone recontouring or osseous procedure at the time of surgical therapy); *(2)* retrospective studies, case reports, animal research, or studies with < 10 treated individuals per arm; *(3)* studies with a follow-up time of < 12 months; and *(4)* those with a specific population cohort (eg, studies recruiting only certain individuals such as smokers or diabetic patients, etc).

Information Sources and Search Strategy

A detailed computerized and systematic literature search was conducted in the following electronic databases: The National Library of Medicine (MEDLINE via PubMed), EMBASE via OVID, the Cochrane Central Register of Controlled Trials, Latin American and Caribbean Health Sciences Literature, Web of Science, and Scopus. To examine any unpublished trials, the grey literature, nonprofit reports, government research, and other materials were also electronically explored via searching in ClinicalTrials.gov and OpenGrey. Additional details are described in the Appendix Tables 1 to 3 (available at the end of this article).

Study Selection and Data Retrieval

Two calibrated review authors (S.B. and H.S.) independently performed the selection process of the studies twice. If needed, a third reviewer (A.M.) was consulted. Details are provided in Appendix Tables 1 to 3.

Assessment of Methodologic Quality and Risk of Bias

The assessment of methodologic quality and risk of bias of the included studies was performed independently (and in duplicate) by two examiners (S.B. and H.S.) according to the recommended approach by the Cochrane Collaboration group[30] (see Appendix Table 2).

Synthesis of Results and Statistical Methodology

The main methodology of the current review was based on a quantitative analysis planned from RCT-derived data. Transitivity was assessed to ensure the possibility of conducting a network meta-analysis-based model (see Appendix Table 3).

A frequentist mixed-modeling approach to network meta-analysis[31–34] was then used to model the aggregate data for the primary outcomes of PPD reduction (in millimeters), Rx MBL gain (in millimeters), BoP reduction (percentage), and SUP reduction (percentage). The secondary outcomes that were assessed included an increase in MREC (in millimeters) and disease resolution (when data was available). It was planned to assess changes in the stated outcomes after surgical reconstructive therapy for peri-implantitis in the broad sense of comparing reconstructive therapies (where regenerative treatment is attempted) to nonreconstructive treatment (such as open flap debridement alone), as

well as to explore any potentially relevant variables that could influence therapeutic outcomes. In addition, the individual components of the rendered treatments (ie, the specified surgical reconstructive approach in each study arm) were modeled per their type of chemical and mechanical decontamination or detoxification method, the choice of bone replacement graft (whether autogenous, allogeneic, xenogeneic, synthetic, titanium particles, or none), the use of a barrier membrane, and management of the implant suprastructure (whether crown removal occurred and if the healing protocol was submerged or transgingival). Similar to methodologies applied in our work,[31,34–36] study arms were weighted by their effective sample size treated (ie, the number of treated defects per study arm) and clustered by publication cohort. For studies that used the same patient population (ie, different follow-up reports of the same original research), only one report with the most informative and complete data was used in the present analyses. Baseline demographics and clinical characteristics of the defects and patients were all accounted for in all models by inclusion of fixed covariates, and their influence on each outcome was assessed. Random effects were included to capture unique intercepts for study, study arms, as well as random slopes for study by time and study arm by time.

The construction of the models was performed by testing a series of specifications of random and fixed effects via different model structures, using primarily the Akaike information criterion as evidence for the model that best fit the data.[37] Confidence intervals (CIs) were produced, and a *P* value threshold of $< .05$ was set for statistical significance. The statistical analyses were performed by an author (S.B.) with experience in network meta-analyses and linear mixed models using a specified software and the following statistical packages: lme4,[38] lmerTest,[39] dplyr,[40] and tidyr.[41] The igraph[42] and ggplot2[43] packages were used for producing the geometry of the network plot to visualize the in-study contrasts and the existing relationships among treatment arms.

Additional details of the applied methodology are provided in Appendix Tables 1 to 5 (available at the end of this article).

Grading the Certainty of Evidence

In assessing the certainty of evidence of the produced quantitative results, we employed a slightly modified approach to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.[44] Given the nature of our analysis, which used a mixed-model-based regression network meta-analysis rather than traditional pairwise meta-analyses or conventional networks, we adapted our modification to suit this context. Our assessment focused on the following key domains: *(1)* estimate—95% CIs alongside associated *P* values; *(2)* study design—the rigor and appropriateness of the included studies; *(3)* population characteristics—sample size and the number of implants to gauge the representativeness of the study populations; *(4)* follow-up duration—the adequacy of the observational period for capturing relevant outcomes; *(5)* RoB—the methodologic quality of the included studies; *(6)* inconsistency—the agreement or consistency among study reports; *(7)* indirectness—the relevance and applicability of the evidence to the research question; *(8)* imprecision—the precision of effect estimates, particularly in relation to CIs and the sample size; and *(9)* other relevant considerations specific to our study context.

In culmination, the overall certainty of evidence with regards to each primary outcome of the study across the above-mentioned domains was assessed to be categorized as "very low," "low," "moderate," or "high."

RESULTS

Search Results and Study Selection

The electronic and manual search resulted in a total of 8,026 records, which was reduced to 4,464 after duplicate removal. These articles were then subjected to screening of titles and abstracts. Based on the predetermined inclusion criteria, a total of 40 publications could be included (18 RCTs and 22 non-RCTs). The search process is shown in Fig 1 and described in detail in Appendix Tables 1 to 3.

Characteristics of the Included Research and Qualitative Results

From the overall search strategy and inclusion of studies, 18 articles described cohorts from 12 RCTs,[14,15,19,45–59] and 22 articles were non-RCTs.[18,60–80] It was planned that data from non-RCT studies would be analyzed descriptively. Accordingly, among the 22 non-RCTs, 16 were single-arm studies (case series) and 6 were controlled trials.[69,70,73–76] Moreover, five of the studies[70,72–75] were follow-up reports of previously published original cohort studies.[69,71,76] A total of 15 studies[18,60,61,63–68,74–76,78–80] were conducted in a university setting, whereas 7 were conducted in private practices.[61,62,69–73]

With regard to the treated defect morphology, only 11 out of 16 studies described the characteristics of the treated defects.[18,60,61,63,66–68,71,76,79,80] Among these articles, most included crater-like or circumferential defects.[18,60,61,66,67,79] To break it down further, eight articles included a combination of different types of defects,[60,63,66–68,71,76,80] and 11 studies[62,64,65,68–70,73–75,77,78] did not specify or were unclear regarding this aspect. A

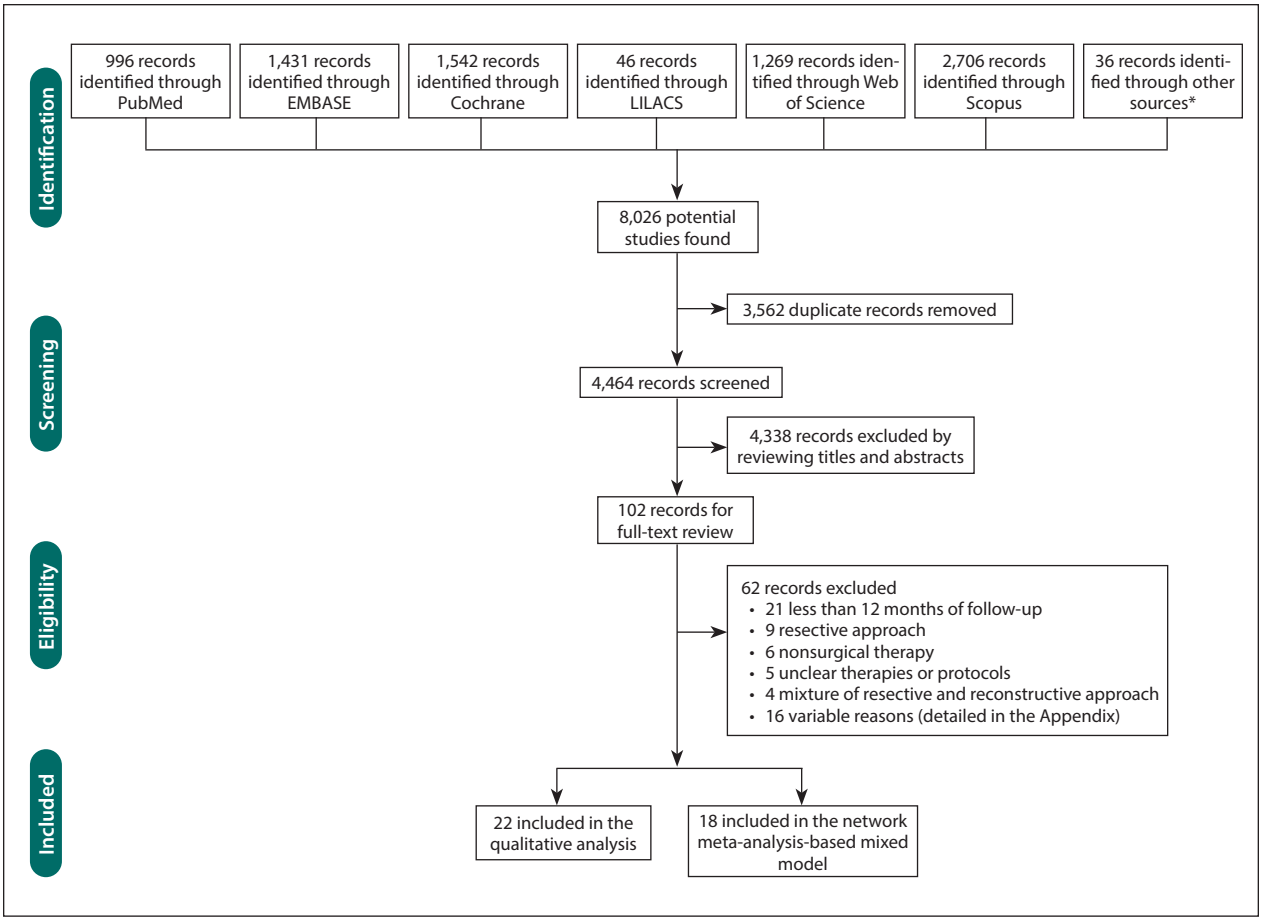

Fig 1 The computerized systematic and manual literature search process for screening articles to identify the included studies. * refers to search in the grey literature.

submerged healing approach, via primary closure, was used in three studies,[18,67,77] while the remaining studies used a nonsubmerged protocol. Appendix Table 1 provides a comprehensive description of the included non-RCT prospective studies with their respective main findings and conclusions. Further descriptions and an analysis of the included studies categorized by the graft material used are provided in Appendix Tables 2 and 3.

Appendix Table 2 outlines the study characteristics of the included RCTs in detail. Most of the reports described a single-center RCT that was conducted in a university setting, but a few were conducted in a private practice setting. As per our prespecified inclusion criteria, all articles had at least a 12-month follow-up after the surgical therapies, with four articles[45,47,52,53] having a longer follow-up recall. In addition, most studies also obtained additional time points (aside from the 12-month recall), and the data were also considered for statistical analysis. Despite all studies having a fundamentally similar definition of disease for peri-implantitis, differences were present among their treated and analyzed peri-implant bone defect morphology. Except for three trials,[14,15,19] all articles had their protocols registered in an online database.

Appendix Table 3 displays the outcomes of the RCTs. Most studies assessed PPD reduction as the primary clinical outcome, with some also focusing on Rx MBL changes. Aside from providing the mean PPD or MBL values per implant, some studies also assessed the most severe sites (such as PPD or Rx MBL at the deepest site). BoP and SUP were expressed mostly in terms of percentages of sites presenting with a positive value at each time point and were also measured across trials. Other outcomes included the number of "disease-free implants" as a result of surgical therapy, which was referred to as "disease resolution" or "success of therapy" among trials. Patient-reported outcomes were also evaluated among a few cohorts.

Assessment of the Risk of Bias

The quality assessment and the risk-of-bias report of the included RCTs and non-RCTs is presented in detail in Appendix Table 4. The final results of the risk-of-bias assessment for the RCTs were included in the quantitative analysis.

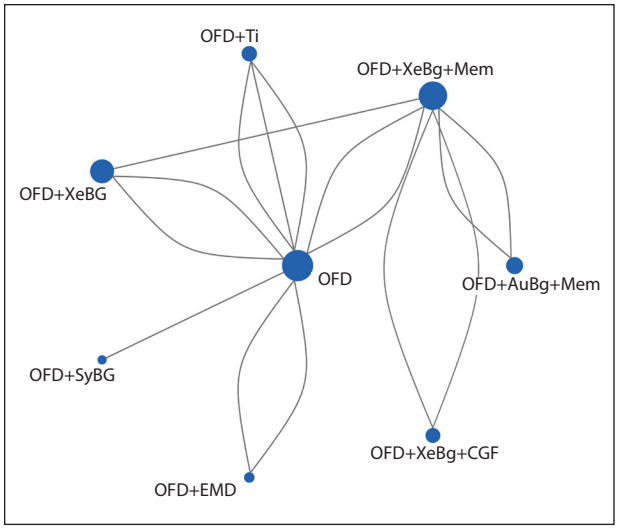

Fig 2 Network plot visualizing the observed comparisons among the selected randomized trials. *Solid lines* connect treatments that are directly compared in at least one study (compared head-to-head in at least one RCT). Studies contributing with only one arm are not presented. Distances are for plot clarity alone, and the node size is proportional to the number of treated sites. AuBG = autogenous bone graft; CGF = concentrated growth factor; EMD = enamel matrix derivative; Mem = collagen membrane; OFD = open flap debridement; SyBG = synthetic bone graft; Ti = titanium particles; XeBG = xenogeneic bone graft.

Quantitative Results and Analysis Through the Mixed-Model Network Meta-analysis

Figure 2 illustrates the direct treatment comparisons among the included RCTs—from the network-based model—and Fig 3 presents the relationships between the segregated treatment components of the included trial arms and the standardized levels of PPD reduction and Rx MBL gain. Note that each line represents the treatment arm of an included study, and the segregated treatment components shown in the plot demonstrate the main structures (fixed effects) of the mixed models. Alloplast and titanium-based materials were excluded from the present study beyond this point due to their observed non-monotonicity, high disparity across their limited data, and reduced clinical value with regard to treatment.

PPD reduction

Based on the included studies,[14,15,19,45,48–51,53–59] the model showed a statistically significant PPD reduction of 2.88 mm (95% CI [2.49–3.28]; $P < .001$). This indicated a significant reduction in PPD as a result of the included therapies among all study arms.

Within the additive structure of the model (having the segregated treatment components as shown in Fig 3), the adjunct use of titanium brushes during surgical debridement (0.45 mm; 95% CI [0.15–0.75]; $P < .01$) as well as the use of an allograft (2.61 mm; 95% CI [1.66, 3.55]; $P < .001$) and xenograft (0.91 mm; 95% CI [0.62, 1.21]; $P < .001$) demonstrated a statistically significant association with PPD reduction. Nevertheless, no significant effect from adjunct chemical disinfectants could be noted. The effect of incorporating a barrier membrane was weakly associated with PPD reduction, and while demonstrating trends for improvement in the outcome, it lacked statistical significance (0.19 mm; 95% CI [–0.06, 0.45]; $P = .09$).

Initial severity of PPD among study arms was also statistically significant (0.62 mm; 95% CI [0.46, 0.77]); $P < .001$). It depicted such a positive association between PPD reduction and the severity of mean PPD at baseline that deeper sites on average obtained a higher reduction in PPD. Similarly, baseline Rx MBL also predicted PPD reduction with a positive association (0.38 mm; 95% CI [0.14, 0.62]; $P = .02$), whereas the defect morphology itself did not seem to be associated with this outcome (95% CI [–0.02, 0.003]; $P = .17$).

Time was also found to have a significant role (–0.019 months; 95% CI [–0.03, –0.007]; $P < .01$), which indicated a small but linear relapse in the initial reduction of PPD. Smoking (as the percentage of smoking individuals per study arm) also demonstrated a significant negative association with PPD reduction (–0.02%; 95% CI [–0.03, –0.009]; $P < .01$), while baseline keratinized tissue width (KTW) showed a positive statistically significant effect in the model (0.65 mm; 95% CI [0.47, 0.83]; $P < .01$), indicating that sites with higher initial KTW led to greater PPD reduction.

Radiographic MBL gain

When Rx MBL gain was evaluated based on the included studies,[14,15,19,45,46,48–59] the model revealed significant associations with certain factors. Notably, the use of bone substitutes such as allograft particulates (1.14 mm; 95% CI [0.49, 1.78]; $P < .001$) and xenogeneic bone (0.43 mm; 95 % CI [0.11, 0.74]; $P = .01$) had statistically significant higher outcomes. In addition, mechanical debridement via titanium brushes was also significantly associated with increased Rx MBL (0.12 mm; 95% CI [0.002, 0.255]; $P = .03$).

Interestingly, time did not emerge as a significant factor in this model (0.004 ; 95% CI [–0.005, 0.01]; $P = .361$). However, the application of a barrier membrane at the time of augmentation was significantly associated with a positive effect (0.56 ; 95% CI [0.22, 0.903]; $P < .001$). Smoking was also found to be associated with reduced outcomes (–0.01 ; 95% CI [–0.01, –0.01]; $P < .001$). Furthermore, removal of implant suprastructures at the time of surgical therapy (0.48 ; 95% CI [0.13, 0.84]; $P = .02$), along with employing a primary wound closure and a submerged healing approach, were both

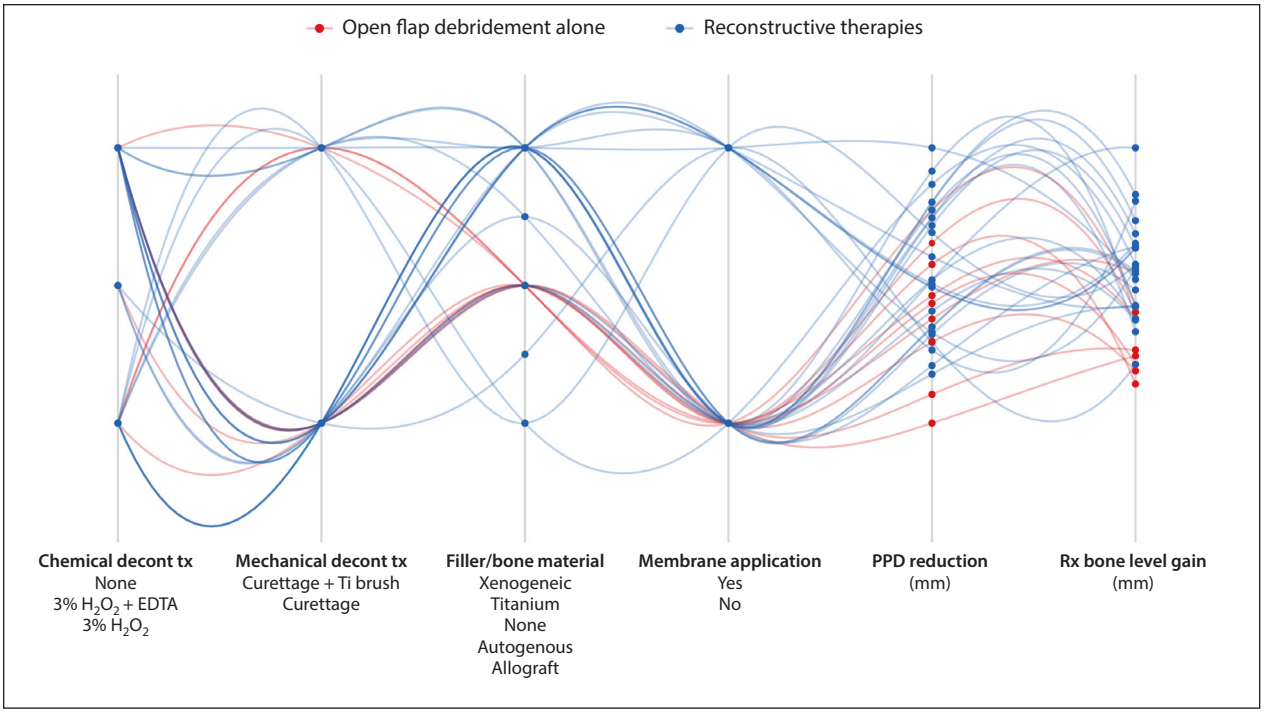

Fig 3 Parallel coordinates plot depicting the relationship between the segregated treatment components of the RCTs and the outcomes of mean PPD reduction and mean Rx MBL gain. Quantitative values on the vertical axes for the mentioned outcomes are scaled independently to visually encompass the range of data and display the standardized values of the corresponding variable. Note that points of the same study arms are connected with color-coded lines to display the trend among study arms of open flap debridement *(red line)* and reconstructive control groups *(blue line)*. EDTA = ethylenediaminetetraacetic acid; H_2O_2 = hydrogen peroxide; tx = therapy.

associated with improved outcomes (0.47 ; 95% CI [0.12, 0.82]; *P* = .01). The percentage of treated circumferential defects among trials was highly associated with enhanced MBL gain (0.04 ; 95% CI [0.04, 0.04]; *P* < .001), and baseline KTW was also found to positively affect the outcomes (0.32 mm; 95% CI [0.01, 0.64]; *P* = .03).

BoP reduction

With regard to BoP reduction (based on studies that had provided this outcome as numerical values or percentages),[14,15,19,45,48–54,56,57] the only statistically significant factors in the model were the initial BoP (1.02%; 95% CI [0.09, 1.95]; *P* = .03) and removal of the suprastructure at the time of surgical therapy (6.65%; 95% CI [2.88, 10.42]); *P* = .01).

SUP reduction

Among the studies from which data could be pooled,[14,15,48,50,53,54,56,57] it was shown that baseline SUP (0.57%; 95% CI [0.37, 0.77]; *P* < .001) and baseline BoP (2.99%; 95% CI [2.49, 3.49]; *P* < .001) were both reported to be associated with SUP reduction.

MREC

Among the assessed RCTs,[15,19,48–50,53,55,57,58] the model found that the application of allograft bone (–0.32 mm; 95% CI [–0.52, –0.11]; *P* < .01) and xenogeneic bone particulates (–0.44 mm; 95% CI [–0.55, –0.33]; *P* < .001) both could reduce changes in mucosal recession after surgical therapy. In addition, baseline KTW was also significantly associated with reduced changes in MREC (–0.12 mm; 95% CI [–0.23, –0.01]; *P* = .03).

Certainty of Evidence

When using the modified GRADE approach (based on the assessment of risk of bias, inconsistency, indirectness, and imprecision across the included studies), the overall certainty of evidence varied across outcomes. PPD reduction exhibited a high level of certainty (n = 992; moderate risk of bias), while Rx MBL gain (n = 1,043; moderate risk of bias) and BoP resolution showed moderate certainty (n = 1,081; moderate risk of bias). However, the resolution of SUP had a lower level of certainty (n = 355; moderate risk of bias).

DISCUSSION

Despite peri-implantitis being one of the most common challenges in dentistry today, there has been no therapy or management protocol found to predictably treat this disease. When considering a reconstructive

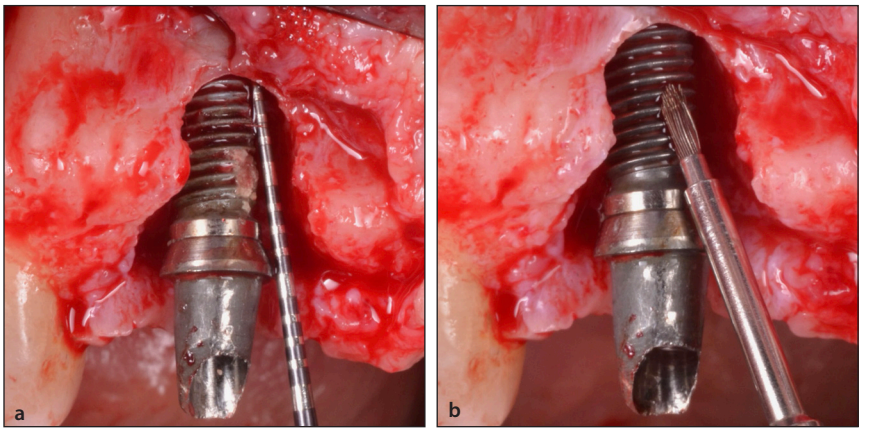

Fig 4 Implant surface decontamination with the use of titanium brushes. *(a)* Intraoperative photo after flap reflection showing the implant with peri-implantitis prior to debridement. *(b)* Clinical image of the implant and the titanium brush used for adjunct debridement.

approach, the many different components of these algorithms—from method(s) of decontamination to graft material to biologic-barrier membrane selection(s)—can each have a qualifying effect on the expected clinical outcomes, which may partially explain the failure to gain a consensus for the best possible approach. In the current review, our aim was to adopt an evidence-based and data-driven approach to examine the various aspects of surgical reconstructive treatment for peri-implantitis. By conceptualizing a mixed-modeling approach to data analysis, we aimed to underpin the research focused on this area by collecting eligible RCTs with similar methodology and interchangeable inclusion criteria to provide a dataset that could be subject to quantitative analysis.

Through the latitudes provided by mixed models, we analyzed a substantial amount of data to contrast and, in essence, isolate the treatment effects from the variable components inherent to each treatment arm (as shown in Fig 3). This allowed for exploration of the relative effects and impact of the broad category of the applied chemotherapeutic and mechanical decontamination approaches, the constituents of the augmentation therapies (ie, the bone replacement grafts, whether a barrier membrane was utilized, the impact of a biologic agents), as well as many other pertinent factors on different therapeutic outcomes.

Summary of Main Findings

Overall, our results suggest that a surgical reconstructive approach for peri-implantitis, when compared to nonreconstructive therapies (ie, open flap debridement without any additional attempt for reconstruction of the bony defect), was effective in improving the PPD reduction and was even more effective in the short-term radiographic bone gain. With regard to reduction of BoP and SUP, there seemed to be no additional benefit from employing a reconstructive approach. Furthermore, it appeared that certain baseline variables such as PPD, initial severity of the radiographic bone defect, the defect morphology, and KTW play a significant role in the overall clinical outcomes of surgical treatment of peri-implantitis (whether a reconstructive approach is employed or not). In addition, despite the specific rendered therapy, it was demonstrated that treatments tend to have a slight but statistically significant relapse in the outcomes over time; however, this effect was reduced by half when a reconstructive therapy was used with either a particulate allograft or xenograft.

Implant Surface Decontamination and Peri-implant Defect Debridement

As with periodontal disease, the initial aim of a surgical procedure for peri-implantitis is to provide access for thorough debridement and decontamination of the affected implant surface and remove bacterial biofilm and any calcified deposits or etiologic agents, thus detoxifying the implant surface. A variety of tools and protocols are used to aid this crucial step, which can be categorized under chemical and mechanical decontamination. In our analysis, we were able to explore both approaches within the confines of our dataset and the selected trials.

Among chemical decontamination methods, we observed three primary categories: no local chemical decontamination, 3% hydrogen peroxide (H_2O_2) alone, and its combination with EDTA. While there are some reports in favor of using the stated agents in periodontal and peri-implant disease therapy,[73,81,82] our analysis failed to yield a significant effect from their adjunct use in any of the outcomes. It is important to bear in mind that all the trials that used these agents had done so after a series of mechanical therapy with hand and/or ultrasonic instrumentation that was followed by sterile saline irrigation of the defects after use of the chemical agent.

With regard to mechanical decontamination methods, most of the studies mentioned employing a similar approach of hand and ultrasonic instrumentation with the use of curettes (either stainless steel or

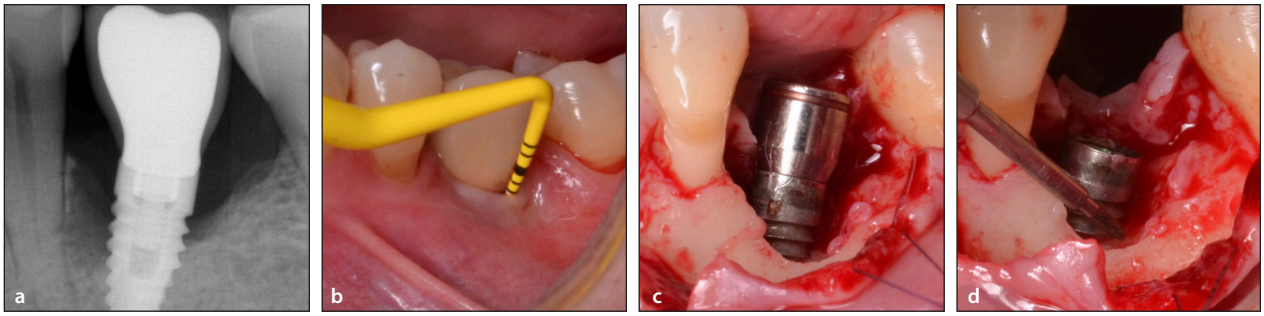

Fig 5 Surgical treatment of peri-implantitis for a malpositioned implant facilitated by the removal of the implant suprastructure/prosthesis. *(a and b)* Preoperative photo and radiograph of the affected implant with peri-implantitis showing signs of marginal mucosal inflammation, radiographic bone loss, and deep PD. *(c)* Intraoperative photo of the implant after flap reflection and removal of the implant crown. *(d)* Removal of all implant suprastructures to aid with decontamination of the implant surface and debridement of the defect. Note the increased access and visibility that it provided not only after removal of the implant crown but also with removal of the healing abutment.

titanium),[14,15,19,45–47,49–53,56,59,83] with some also using titanium brushes.[48,54,55,57,58] Interestingly, our analysis revealed that the adjunct application of titanium brushes demonstrated a statistically significant positive effect on the outcomes of PPD and SUP reduction, as well as Rx MBL gain (Fig 4).

It should be noted that the effect of other local chemical agents (such as citric acid, etc) or local antibiotics (eg, locally delivered tetracycline) remain to be explored, as well as other mechanical remedies such as implantoplasty procedures or the application of power-driven air-polishing devices, because they could not be included in the current analysis.

Augmentation Approach and the Applied Biomaterials

The selection of a biomaterial or bone graft substitute for filling the peri-implant defect after decontamination can vary based upon a multitude of factors. Among the retrieved data from our literature search, we noticed a predominant use of xenograft substitutes, followed by allogeneic bone materials, and significantly less use of synthetic bone substitutes. For the quantitative analysis, due to limited data from RCTs on synthetic agents (being solely tested among a single study cohort), the assessment and comparison of bone replacement grafts remained among materials of autogenous, allogeneic, xenogeneic, and titanium origin. Nevertheless, the application of xenogeneic and allogeneic grafts (in an increasing order of effect) both led to significantly increased PPD reduction and Rx MBL gain and a decrease in MREC after the surgical interventions. With regard to the application of a barrier membrane, a statistically significant positive effect was seen for the outcome of Rx MBL gain, while there was weak evidence supporting its benefit when considering the outcome of PPD reduction.

Removal of Implant Suprastructures

The removal of implant suprastructures or prostheses can serve two main purposes: *(1)* provide enhanced accessibility for peri-implant debridement, and *(2)* help to obtain primary wound closure by submerging the implant and allowing for undisturbed healing in a closed environment (ie, the submerged approach)[84] (Fig 5). In our analysis, we found both effects to be statistically associated with improved therapeutic outcomes when the prosthesis was removed solely to aid in decontamination and when primary wound closure was obtained. Our results indicate that the reconstruction of peri-implant bone defects can be obtained through both non-submerged and submerged approaches, regardless of whether the suprastructure is removed or not. However, whenever feasible, the removal of implant crowns or prostheses should be considered to allow for greater access to the implant's surface and the osseous defects during detoxification. In the pursuit of long-term success and to prevent treatment relapse, when prostheses are removed, these can be carefully recontoured (or ideally refabricated) to facilitate at-home hygiene care and reduce chances for reinfection. Early on, this theory was tested in a preclinical model and demonstrated that submerged healing improved the surgical treatment outcomes in terms of radiographic and histomorphometric findings, particularly bone-to-implant contact.[85] Despite the advantages of this approach, which have also been shown in human clinical research,[18] potential drawbacks of submerged healing must be considered. These drawbacks include the necessity to remove the prosthesis, which translates into increased treatment time, costs, and an interim prosthesis (in esthetic areas). In addition, coronal advancement of the flap for achieving primary wound closure can also result in distortion of the mucogingival margin, a reduction of KTW, and potentially increased postoperative morbidity. Thus, readers must bear these aspects in mind when opting for the surgical approach.

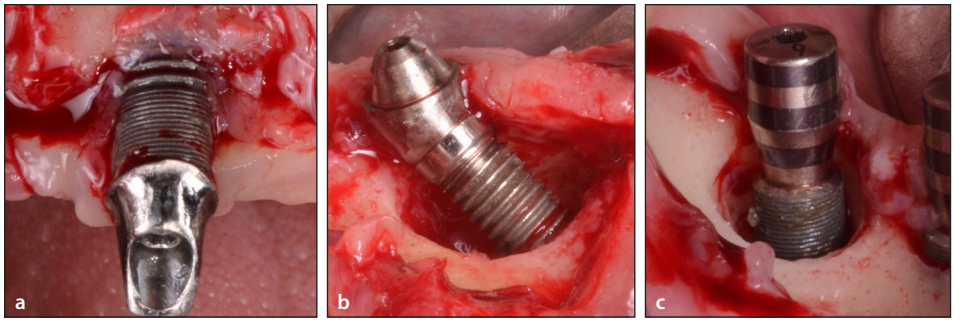

Fig 6 Intraoperative photos of different implants with peri-implantitis at the time of surgical therapy showing *(a)* noncontained, *(b)* partially contained, and *(c)* well-contained defect morphology.

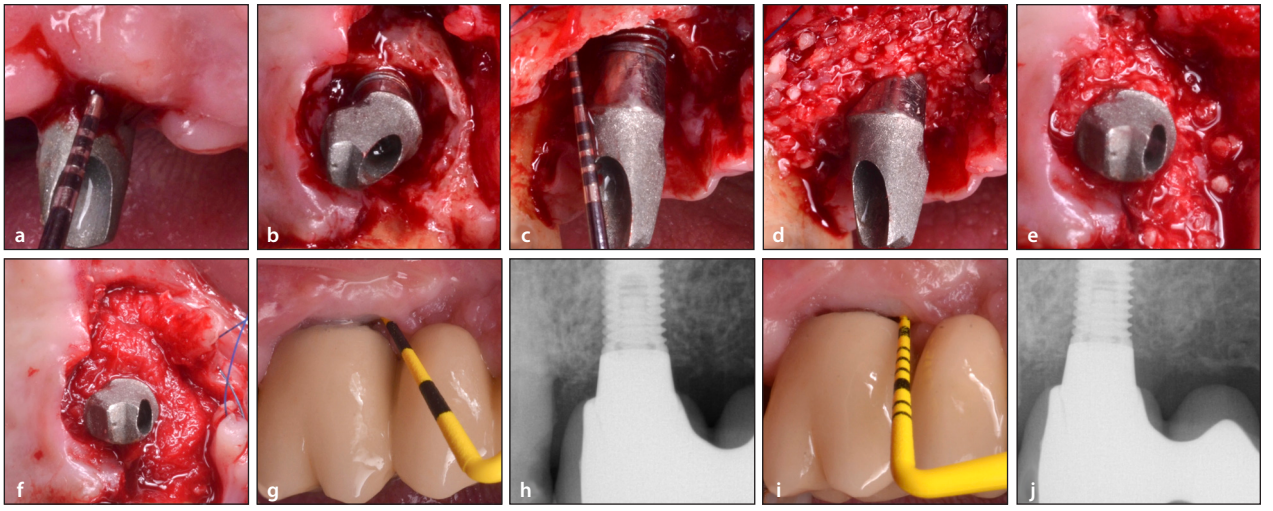

Fig 7 Surgical reconstructive therapy for an implant with peri-implantitis. *(a)* Visible initial deep PD and mucosal inflammation. *(b)* Intraoperative occlusal view showing the resultant peri-implant bony defect surrounding the affected implant. *(c)* Assessment of the infrabony component of the defect prior to augmentation and after decontamination. *(d and e)* Frontal and occlusal views of the implant at the time of augmentation followed by *(f)* stabilization of the applied mixture of the demineralized and mineralized bone allograft. *(g and h)* Clinical and radiographic images of the treated implant 2 years after surgical reconstructive therapy. Note that a wide band of keratinized tissue was present at baseline, which has likely contributed to the outcome of disease resolution and its maintenance.

Local/Systemic Factors Pertinent to the Clinical Outcomes

Among additionally explored factors, we found that an increased percentage of smokers in the patient population of study arms negatively affected the outcomes of PPD reduction and Rx MBL gain. Additionally, it is important to note that when other factors were accounted for in the models, both age and sex were not found to be associated with any of the outcomes. The initial severity of the peri-implantitis defects, in terms of baseline PPD and MBL, were significantly associated with PPD reduction; for example, deeper PPD and Rx MBLs predicted an increased reduction of PPD. Similarly, inclusion of circumferential defects among study arms (in terms of the percentage of the total treated peri-implantitis sites) was highly associated with increased Rx MBLs (Fig 6). Next, despite a defect angle being recently reported to significantly predict reconstructive outcomes,[86] this aspect was sparsely examined across the included publications. The presence and higher values of KTW were also shown to play a beneficial role in the following outcomes: PPD reduction, MBL gain, and MREC reduction (Fig 7). Moreover, the beneficial roles from KTW have been demonstrated throughout the literature,[36,87] and its augmentation has been suggested to minimize disease recurrence in scenarios exhibiting a lack of KTW associated with peri-implantitis–related defects.[88]

Limitations

It should be noted that because the aim of this review was to explore the effect of reconstructive therapies, we did not include any studies that performed a resective approach or referenced osseous recontouring or apically positioning the flap at the time of the surgery. For the same reason, any study that included peri-implantitis defects with a flat bony architecture was not considered. Note that regenerative therapies for peri-implantitis were specifically indicated for infrabony defect management.[15,89–92] In addition, merging data from resective approaches to studies that only performed reconstructive surgery would confound the

analysis. Therefore, readers should note that our results were bound by these explicit inclusion criteria, and the fact that the analyzed defects were from adequately designed RCTs may not necessarily reflect the morphology of all diseased implants (such as misaligned implants or those that are positioned far too buccal, etc). Furthermore, our analysis of the "quality" of trials (as per RoB-293 rubrics) showed some methodologic concerns to be present among the included RCTs. It should be noted that three trials[14,15,19] did not report protocol registration in their respected published reports, which can induce biases regarding outcome assessment and more. In addition, one study[94] exhibited a high risk of bias due to concerns regarding deviations from the intended intervention and management of missing outcome data. The Appendix tables available at the end of this article provide additional details regarding the risk-of-bias assessments and other potential limitations of the present study that need to be considered.

CONCLUSIONS

Based on the current available literature and the limitations within this research, the following conclusions can be drawn:

1. Surgical reconstructive modalities to manage peri-implantitis–related infrabony defects outperform nonreconstructive treatment modalities in terms of PPD reduction, MREC reduction, and Rx MBL gain in cases of contained and particularly circumferential bony defects. Nonetheless, there were no significant differences between the two modalities of treatment for the outcomes of BoP and SUP.
2. With regard to mechanical debridement and implant surface decontamination, the use of titanium brushes after hand and ultrasonic instrumentation appeared to provide additional benefits in clinical outcomes.
3. Adjunct chemical decontamination using H_2O_2 and/or EDTA compared to sterile saline rinse alone did not provide additional benefits.
4. There was support for the application of allografts or xenografts with regard to PPD reduction, MREC reduction, and Rx MBL gain, while the evidence to suggest the use of barrier membranes was weaker.
5. Baseline severity and the bone defect morphology of the peri-implantitis lesion significantly impacted the outcomes of the surgical therapy (notwithstanding whether a reconstructive therapy was performed or not).
6. The presence of KTW plays a significant and beneficial role in the overall clinical outcomes of surgical treatment of peri-implantitis.

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APPENDIX

Appendix Table 1 Characteristics of the Included Nonrandomized Studies in the Qualitative Analysis

Author, study, design, and setting	No. of patients and implants	Follow-up time	Peri-implantitis definition	Peri-implantitis defect morphology (defect site characteristics)	Smoking status? (S, NS, FS)	History of periodontitis
Roos-Jansaker et al[76] (2007), CCT, university	36 patients, 65 implants Group 1: 17, 29 Group 2: 19, 36	1 y	Progressive loss of ≥ 3 threads (1.8 mm) following the first year of healing + BoP and/or PUS	1-wall defects: 14.6% 2-wall defects: 29.2% 3-wall defects: 43.8% Circumferential defects: 10.4% Not classified: 2.1%	Group 1: 12 S, 1 NS, 4 FS Group 2: 12 S, 2 NS,4 FS	18 patients: tooth loss due to periodontitis 2 patients: tooth loss due to other reasons 16 patients: unknown etiology
Roos-Jansaker et al[74] (2011), CCT, university	32 patients, 56 implants Group 1: 29, 17 Group 2: 27, 15	3 y	Same as the 2007 study	NR	Group 1: S 70.6% Group 2: S 68.4%	Same as 2007 study
Roos-Jansåker et al[75] (2014), CCT, university	25 patients, 45 implants Group 1: 23, 13 Group 2: 22,12	5 y	Same as the 2007 study	NR	Group 1: S 76.9% Group 2: S 66.7%	Same as 2007 study

Decontamination method	Reconstructive approach	Regenerative materials	PD reduction, mean ± SD (n)	BoP and SUP reduction	MBL gain (mean ± SD)	Disease resolution or success criteria	Reported conclusion
Granulomatous tissue removed with titanium instruments. The threads were cleaned from mineralized calculus and the implant surface was cleansed using hydrogen peroxide (3%), followed by profuse rinsing with saline (no implantoplasty).	Nonsubmerged with prosthesis removal	Group 1: alloplast + collagen membrane Group 2: alloplast	PDR: Group 1: 2.86 ± 2.00 (range: 0–9) Group 2: 3.44 ± 1.58 (range: 0–9)	1 y: Group 1: 0: 78.4% 1: 12.1% 2: 9.5% 3: 0% Group 2: 0: 75% 1: 9.3% 2: 15.7% 3: 0% /NR	Group 1: 1.52 ± 1.16 (−0.6; 3.9) Group 2: 1.44 ± 1.27 (−0.9; 4.2)	NR	It is possible to treat peri-implant defects with a bone substitute, with or without an absorbable membrane (membrane did not show superior outcomes compared to no-membrane group).
Same as the 2007 study.	Same as the 2007 study	Same as the 2007 study	Not measured	Not measured	Group 1: 1.6 ± 1.2 Group 2: 1.3 ± 1.3	NR	Defect fill using a bone substitute with or without a membrane technique in the treatment of peri-implantitis can be maintained over 3 years.
Same as the 2007 study.	Same as the 2007 study	Same as the 2007 study	PDR: Group 1: 3.0 ± 2.4 Group 2: 3.3 ± 2	Not measured	Group 1: 1.5 ± 1.2 Group 2: 1.1 ± 1.2	Radiographic evidence of ≥ 25% bone fill but independent of PD or bleeding status = 66.7% (30/45) Radiographic evidence of ≥ 25% bone fill and with the deepest PD ≤ 5 mm but independent of bleeding score = 62.2% (28/45) Radiographic evidence of ≥ 25% bone fill and with the deepest PD ≤ 5 mm and with BoP score ≤ 1 = 51.1% (23/45)	Both procedures resulted in stable conditions. Additional use of a membrane does not improve the outcome. No implant loss reported.

Appendix Table 1 *(cont)* **Characteristics of the Included Nonrandomized Studies in the Qualitative Analysis**

Author, study, design, and setting	No. of patients and implants	Follow-up time	Peri-implantitis definition	Peri-implantitis defect morphology (defect site characteristics)	Smoking status? (S, NS, FS)	History of periodontitis
Froum et al[62] (2015), case series, private practice	100 patients, 170 implants	2–10 y (mean 3.60 ± 1.86)	BoP + PPD ≥ 5 mm, BL ≥ 3 mm	Peri-implant BL ≥ 3 mm (morphology NR)	19 S, 151 NS (NS defined as smoking < 10 cigarettes/day)	NR, patients received all necessary periodontal treatment prior to the surgery
Roccuzzo et al[71] (2016), case series, private practice	71 patients, 71 implants	1 y	PPD ≥ 6 mm + crater-like defect and no mobility	Ia: 9, Ib: 22, Ic: 14, Id: 13 and Ie: 13	11 S, 64 NS	All patients previously treated for periodontitis
Roccuzzo et al[72] (2021), case series, private practice	51 patients, 51 implants	5 y	Same as the 2016 study	Same as the 2016 study	NR	Same as the 2016 study

Decontamination method	Reconstructive approach	Regenerative materials	PD reduction, mean ± SD (n)	BoP and SUP reduction	MBL gain (mean ± SD)	Disease resolution or success criteria	Reported conclusion
Debridement of implants and osseous defects with graphite curettes or titanium tips. Decontamination: fine bicarbonate powder (60 s), air-abrasive device with contra-angled tip, 60 seconds of irrigation with saline, application of tetracycline 50 mg/dL or minocycline 50 mg/dL for 30 seconds; second exposure to bicarbonate air abrasion for 60 seconds, application of CHX gluconate 0.12% (30–45 s) and reirrigation with saline.	Nonsubmerged	EMD or PDGF + DBBM or allograft If KTW < 2 mm: CTG used as a barrier to contain the material If KTW ≥ 2 mm: collagen membrane instead of CTG	PDR: 5.10 ± 2.20 (range: 2–12)	BoP resolution: 91%	1.77 ± 1.99 mm	NR, 2 implants were lost at 6 months postoperative (98.8% survival rate)	"The results using the layered/ combined regenerative appear to be encouraging."
Titanium curettes for debridement. When necessary—especially in deep, narrow defects—implant surfaces instrumented with a titanium brush at 300 rpm under irrigation. EDTA 24% for 2 min and CHX 1% gel for 2 min followed by sterile saline. No implantoplasty.	Nonsubmerged	DBBM with 10% collagen	PD: Baseline: 7.17 ± 1.61 1 y: 4.24 ± 1.36 PDR: 1 y: 2.92 ± 1.73 (n = 71)	BoP resolution: 53.2 ± 39.4	NR	PD ≤ 5 mm and absence of BoP/SUP: 37 (52.1%) of the 71 implants examined	Lack of evidence of whether the resolution of the peri-implant disease is associated with the defect configuration. Complete resolution did not seem predictable. The clinical decision on whether implants should be treated should be based on several patient-related elements.
Same as the 2016 study.	Nonsubmerged	Same as the 2016 study	PD: Baseline: 6.89 ± 1.58 5 y: 4.06 ± 1.12 PDR: 2.86 ± 0.46	BoP: Baseline: 70.6% ± 34.9 5 y: 17.2% ± 22.1% SUP: Baseline: 15 (29.4%)	NR	5-y survival rate: 80%	The proposed reconstructive treatment resulted in a high 5-year implant survival rate in patients who fully adhered to supportive therapy. The resolution of the peri-implantitis does not seem significantly associated with the defect configuration at the time of treatment.

Appendix Table 1 *(cont)* **Characteristics of the Included Nonrandomized Studies in the Qualitative Analysis**

Author, study, design, and setting	No. of patients and implants	Follow-up time	Peri-implantitis definition	Peri-implantitis defect morphology (defect site characteristics)	Smoking status? (S, NS, FS)	History of periodontitis
La Monaca et al[64] (2018), case series, university/ hospital	34 patients, 34 implants	1, 2, 3, 4 and 5 y	Progressive BL of ≥ 3 mm + BoP and/or SUP	BL of ≥ 3 mm detected on standard intraoral radiographs	25 NS, 9 FS	13 patients: History of periodontal treatment 3 patients: unknown 18 patients: no history of periodontal treatment
Mercadoet al[66] (2018), case series, university/ hospital	30 patients, 30 implants	1, 2, and 3 y	PPD > 4 mm, BoP/SUP + ≥ 20% BL and in function for at least 2 y	Crater- like or circumferential defects	30 NS	13 patients: History of periodontal treatment 3 patients: unknown 18 patients: no history of periodontal treatment Unclear, periodontal treatment provided prior to the surgery as needed

Decontamination method	Reconstructive approach	Regenerative materials	PD reduction, mean ± SD (n)	BoP and SUP reduction	MBL gain (mean ± SD)	Disease resolution or success criteria	Reported conclusion
The implant surface was debrided using an ultrasound instrument and rotating titanium brush, polished with glycine and bicarbonate powders, and then rinsed for 1 min with a sterile saline solution. The implant surface was then decontaminated with 3% hydrogen peroxide for 1 min and with 0.2% CHX solution for 1 min and treated for 3 min with a solution of tetracycline hydrochloride before being washed with sterile saline solution for 1 min (no implantoplasty).	Nonsubmerged	Allograft + collagen membrane	PDR: 1 y: 2.466 ± 0.282 (SE) 2 y: 2.216 ± 0.268 (SE) 3 y: 1.943 ± 0.262 (SE) 4 y: 1.545 ± 0.380 (SE) 5 y: 1.307 ± 0.425 (SE)	BoP: Baseline: 100% 1 y: 32.25% 2 y: 38.24% 3 y: 26.47% 4 y: 38.24% 5 y: 41.18%	1 y: 1.57 (SE 0.28) 2 y: 1.49 (SE 0.25) 3 y: 1.21 (SE 0.25) 4 y: 0.77 (SE 0.34) 5 y: 0.50 (SE 0.37)	No additional marginal peri-implant BL, absence of PD ≥ 5 mm, and absence of BoP/SUP: 1 y: 91% (N = 31) 2 y: 85% (N = 29 3 y: 79% (N = 27) 4 y: 68% (N = 23) 5 y: 59% (N = 20)	At 1-year follow-up, the surgical reconstructive therapy showed clinical improvement and radiographic defect filling. However, the results appeared to be unpredictable over time, due to a progressive decrease in the bone fill of the peri-implant defects and an increase in the mean PD.
The exposed implant threads were debrided using a fine-tip low-power ultrasonic scaler. The implant surface was dried with gauze, and 24% EDTA was applied to all exposed threads for 2 min. The surfaces were then washed with saline solution (no implantoplasty).	NR (possibly nonsubmerged)	DBBM with 10% collagen + EMD + doxycycline	PD: BL: 8.90 ± 1.9 1 y: 3.55 ± 0.50 2 y: 3.50 ± 0.50 3 y: 3.5 ± 0.50	NR	MBL: Baseline: 6.92 ± 1.26 1 y: 2.85 ± 0.73 2 y: 2.62 ± 0.80 3 y: 2.60 ± 0.73	PD ≤ 5 mm, further BL < 10% when compared to baseline bone level; no BoP/SUP and recession (anterior < 0.5 mm and posterior < 1.5 mm) Percentage of treatment success: 56.7% (17/30)	Regenerative treatment of peri-implantitis using a combined mixture of DBBM, EMD, and doxycycline achieved promising results.

Appendix Table 1 *(cont)* **Characteristics of the Included Nonrandomized Studies in the Qualitative Analysis**

Author, study, design, and setting	No. of patients and implants	Follow-up time	Peri-implantitis definition	Peri-implantitis defect morphology (defect site characteristics)	Smoking status? (S, NS, FS)	History of periodontitis
Gonzalez Regueiroet al[63] (2021), case series, university/hospital	43 patients, 43 implants	1 y	PPD > 5 mm, BoP and/or SUP, and BL ≥ 3 mm	Type 1b: 31 (72.1%) Type 3b/c: 12 (27.9%)	22, S 21 NS	Unclear, untreated periodontitis was an exclusion criterion
Wen et al[78] (2022), case series, university	24 patients, 29 implants	8 mo and 1 y	BoP/SUP, increased PDs compared to previous exam, and BL beyond initial remodeling In the absence of previous data: BoP and/or SUP + PPD ≥ 6 mm + ≥ 3 mm BL	NR	5 S (20.8%) (< 10 cigarettes/day)	Active periodontal disease excluded
Wen et al[18] (2022), case series, university	22 patients, 30 implants	8 mo and 1 y	BoP/SUP, increased PDs + BL beyond initial bone remodeling In the absence of previous data: BoP and/or SUP + PD ≥ 6 mm ≥ 3 mm BL	Vertical defect (of at least 3 mm) and surrounding bony walls (ie, a crater-like defects)	7 S (31.8%) (< 5 cigarettes/day)	18 patients with a history of periodontal disease

Decontamination method	Reconstructive approach	Regenerative materials	PD reduction, mean ± SD (n)	BoP and SUP reduction	MBL gain (mean ± SD)	Disease resolution or success criteria	Reported conclusion
The implant surface was debrided with an ultrasonic scaler then decontaminated with 37% orthophosphoric acid and 2% CHX using a dual syringe containing both products. After 2 min, the implant surface was rinsed with sterile saline solution and the implant surface was scrubbed with gauze. Implantoplasty was used at the supraosseous component of the defect and at the buccal and/or lingual dehiscences using large, medium, and fine diamond drills.	Nonsubmerged	Alloplast bone substitute + collagen membrane	PDR: 3.2 ± 2	BoP resolution: 86% SUP: 48.8%	MBL: Baseline: 5.8 ± 2.1 1 y: 3.2 ± 2.2	Absence of BoP and/or SUP, PPD ≤ 5 mm, and no BL > 0.5 mm 1 year after surgery 86%	The surgical approach together with locally delivered antibiotic achieved a high disease resolution rate after 1 year of follow-up and constitutes a viable option for the management of peri-implantitis.
Curettes used to remove all granulomatous tissues followed by implantoplasty on the exposed threads using rotary instruments under copious saline irrigation and application of an air-abrasive device with glycine powders. Tetracycline (250 mg mixed in 2.5 mL saline) applied on the implant surfaces for 3 min.	Nonsubmerged	60% allograft + 20% DBBM + 20% autogenous bone + with a collagen membrane	PDR: 1 y: 1.51 ± 1.17	BoP resolution (1 y): 65.5%	Clinical defect fill (8 mo): 2.33 ± 1.88 Radiographical defect fill (8 mo): 1.63 ± 1.7	NR	The use of a non-submerged approach (with removal of implant crowns) led to significant improvements in clinical (defect fill, PPD, BoP) and radiographic outcomes.
An air-abrasive device with glycine powders was used followed by implantoplasty on the exposed threads with rotary instruments under copious irrigation and the application of tetracycline (250 mg and 2.5 mL).	Submerged	60% allograft + 20% DBBM + 20% autogenous bone + perforated titanium-reinforced nonresorbable dPTFE with fixation screws	PDR: 1 y: 2.93 ± 0.25	BoP resolution: 63.3%	Clinical defect fill (8 mo): 3.22 ± 0.41 Radiographical defect fill (8 mo): 3.47 ± 0.41	NR	Reconstruction of infrabony peri-implantitis defects is feasible with thorough detoxification of implant sites and a submerged regenerative healing approach.

Appendix Table 1 *(cont)* **Characteristics of the Included Nonrandomized Studies in the Qualitative Analysis**

Author, study, design, and setting	No. of patients and implants	Follow-up time	Peri-implantitis definition	Peri-implantitis defect morphology (defect site characteristics)	Smoking status? (S, NS, FS)	History of periodontitis
Yamamato et al[80] (2020), case series, university	12 patients, 12 implants	1 y	PPD > 6 mm with BoP from at least two sites + radiographic infrabony defect depth > 3 mm or > 20%	Class Ic: 2 Class IIIb: 4 Class IIIc: 6	No current smokers were excluded	NR
Behneke et al[60] (2000), case series, university	17 patients, 25 implants	6 mo to 3 y	Progressive crater-like or saucer-shaped defects + PPD > 5 mm No mobility and no peri-implant radiolucency	Crater-like or saucer-shaped and the extent of the defect was not to exceed 90% of the originally osseous anchored part of the implant	NR	NR
Wiltfang et al[79] (2012), case series, university	22 patients, 36 implants	1 y	A vertical BL ≥ 4 mm with circumferential crater defects with loss of oral and vestibular bone at least 1 y after implant placement	Vertical BL amounting a minimum of 4 mm with circumferential crater defects with loss of oral and vestibular bone	NR	NR
Canullo et al[61] (2019), case series, private practice	6 patients, 13 implants	1 y	NR	Circumferential or semi-circumferential peri-implant bony defects	NR	NR
Matarasso et al[65] (2014), case series, university	11 patients, 11 implants	1 y	PPD ≥ 5 mm + BoP + ≥ 2 mm of MBL or exposure of ≥ 1 thread compared with the bone level on a previous radiograph	NR	5 S, 6 NS	All patients had previous history of chronic periodontitis treatment

Decontamination method	Reconstructive approach	Regenerative materials	PD reduction, mean ± SD (n)	BoP and SUP reduction	MBL gain (mean ± SD)	Disease resolution or success criteria	Reported conclusion
Granular tissue removed from the intrabony defect. Debridement and decontamination of the implant surface performed with Er:YAG laser (no implantoplasty).	Unclear (prosthetic components removed in 10 out of 12 implants for surgical procedure)	DBBM	PD: BL: 7.7 ± 1.7 1 y: 4.5 ± 1.1 PDR: 3.2 ± 0.6	BoP: Baseline: 83.3% (10/12) 1 y: 41.7% (5/12)	Bone loss %: Baseline: 47.1% ± 30.5% 1 y: 20.8% ± 21.0% Bone gain: 55.35% ± 9.5%	NR	The combined use of Er:YAG laser and DBBM could be effective for regenerative surgical peri-implantitis treatment.
Curettes plus an air-powder abrasive instrument with sodium carbonate solution for 30 seconds and rinsed with sterile saline.	The implant prostheses were reattached, either directly after augmentation or within a 14-day period afterward	Autogenous block-shaped or particulate bone grafts (from the retromolar or symphysis) with fixation screws	PD: Baseline: median 5.5 mm 1–3 y: median 1.5 to 2.5 mm	NR	Baseline: mean 6.2 mm 1 y, 3 y: 2.3 mm DF: 0.7–6.9 mm	NR	The implant observation period until the first appearance of the lesion seems to be crucial to the effectiveness of the therapy. Early failures appearing within the first 2 years after implant placement showed a more stable therapeutic result over time.
Curettes. The implant surface below the prosthetic reconstruction was smoothed with rotating diamond burs. The implant surface was decontaminated with etching gel.	Nonsubmerged without prosthesis removal	Autogenous graft harvested from mandible or chin region and mixed 1:1 with DBBM	PDR: 1 y: 4 mm [95% CI: 3.3–4.6]	BoP: Baseline: 61% 1 y: 25% SUP: Baseline: 80% 1 y: 8%	MBL: Baseline: 5.1 mm [95% CI: 4.4–5.9] 1 y: 1.6 mm [95% CI: 1.1–2.2] DF: 3.5 mm [95% CI: 2.7–4.3]	NR	For bone defects larger than 4 mm in case of peri-implantitis, this single surgical intervention provided a reliable method to reduce bone defects.
Disinfection with a glycine powder spray and minocycline paste. The inside of the implant connection was cleaned using CHX 0.2%.	Nonsubmerged and prosthetic rehabilitation was removed (1–2 mos after, prosthetic components were re-placed after a microsurgical reopening)	Autogenous bone (from neighboring area using scrapers) + alloplast bone substitute in a 50:50 ratio + collagen membrane	PD: Baseline: 7.8 ± 1.6 mm 1 y: 3.3 ± 1.1 mm PDR: 4.5 ± 0.5 mm	BoP: Baseline: 77.1 ± 11.4% 1 y: 21.1 ± 17.8% BoP resolution: 56% ± 6.4%	MBL: Baseline: 6.1 ± 0.9 mm 1 y: 1.0 ± 0.4 mm DF: 5.1 ± 0.5 mm	NR	The proposed technique might represent a promising result for the treatment of circumferential and semi-circumferential bone defects around implants affected by peri-implantitis.
Curettes and burs on a high-speed handpiece with silicon polishers. Air-driven device with glycine powders and rinse with saline solution.	Nonsubmerged approach without prosthetic suprastructure removal	DBBM + collagen membrane	PD: Baseline: 8.1 ± 1.8 mm 1 y: 4 ± 1.3 mm PDR: 4.1 ± 0.5 mm	BoP: Baseline: 19.7% ± 40.1% 1 y: 6.1% ± 24% BoP resolution: 13.6% ± 16.1%	MBL: Baseline: 3.5 ± 3.5 mm 1 y: 0.5 ± 1.1 mm Bone fill: 3 ± 2.4 mm Radiographic fill: 93.3% ± 13%	NR	A combined regenerative approach for the treatment of peri-implant defects yielded positive outcomes in terms of PPD reduction and radiographic defect fill after 12 months.

Appendix Table 1 *(cont)* **Characteristics of the Included Nonrandomized Studies in the Qualitative Analysis**

Author, study, design, and setting	No. of patients and implants	Follow-up time	Peri-implantitis definition	Peri-implantitis defect morphology (defect site characteristics)	Smoking status? (S, NS, FS)	History of periodontitis
Monje et al[67] (2020), university	15 patients, 27 implants	1 y	BoP and/or SUP + PPD ≥ 6 mm, BL ≥ 3 mm	Crater-like defects lacking buccal bone (Class Ib-Class IIIc) and with BL < 50% of the total implant length	No	No active periodontitis
Obreja et al[68] (2022), university	20 patients, 28 implants	1 and 2 y	BoP and/or SUP + PPD ≥ 6 mm + radiographic MBL, interproximal bone levels ≥ 3 mm apical of the most coronal portion of the infrabony part of the implant	An intrabony defect component of ≥ 3 mm as detected on radiographs: Ib: 3.4% Ic: 25% Ie: 14% Combined (suprabony and intrabony components): 57.6%	Heavy smokers were excluded	NR
Roccuzzo et al[69] (2011), private practice	26 patients, 26 implants Control: TPS Test: SLA	1 y	Peri-implantitis crater-like lesion with + PPD ≥ 6 mm and no implant mobility	NR	4 S	All patients had been treated for periodontitis
Roccuzzo et al[73] (2017), private practice	24 patients, 24 implants TPS: 12 SLA: 12	7 y (follow-up study)	Same as the 2011 study	NR	4 S	Same as the 2011 study

Decontamination method	Reconstructive approach	Regenerative materials	PD reduction, mean ± SD (n)	BoP and SUP reduction	MBL gain (mean ± SD)	Disease resolution or success criteria	Reported conclusion
Curettes and implantoplasty for supracrestal defects. Surface detoxification with 3% hydrogen peroxide (2 min) and irrigation with 0.12% CHX.	Submerged	Autogenous bone graft (from neighboring zone of the recipient site) with DBBM in 1:1 ratio + collagen membrane	PD: Baseline: 6.3 mm (5.3–8.3) 1 y: 2.6 mm (1.7–5.3) Mean change = 3.7 mm	mBI: Baseline: 1.6 (0.4–2.5) 1 y: 0.05 (0.0–0.5) SUP: Baseline: 59.2% 1 y: 0%	MBL: Baseline: 5.3 mm (2.1–11.1) 1 y: 3.0 mm (0.3–5.4) DF = 2.3 mm	Absence of BoP and/or SUP on gentle probing (0.15–0.2 Ncm) PD ≤ 5 mm No radiographic progressive BL within the SE (± 0.5 mm)	The proposed surgical approach followed by submerged healing to reconstruct peri-implant bone defects may offer one therapeutic option for failing dental implants.
Titanium brushes and implantoplasty with diamond burs and copious irrigation with saline.	Nonsubmerged	DBBM + collagen membrane	PD: Baseline: 4.66 ± 1.4 1 y: 3.54 ± 0.9* 2 y: 3.8 ± 1 PPDR: 1 y: –1.1 ± 1 (*P* = .003) 2 y: –0.86 ± 1 (*P* = .02)	BOP (%): Baseline: 65 ± 35 1 y: 11 ± 18* 2 y: 21 ± 28* BoP SUP: Baseline: 39% 1 y: 4% 2 y: 7%	NR	NR	Peri-implant tissues revealed minor volumetric changes at 12 and 24 months after combined surgical therapy.
Plastic curettes, EDTA 24% (2 min) and a CHX 1% gel (2 min), and saline rinse.	Nonsubmerged	DBBM + CTG if the area lacked keratinized tissue	PD (mm): Control: Baseline: 7.2 ± 1.5 1 y: 5.1 ± 2 (0.001) Test: Baseline: 6.8 ± 1.2 1 y: 3.4 ± 1 (0.003) PDR: Control: 2.1 ± 1.2 Test: 3.4 ± 1.7 (0.04)	BoP reduction: Control: 33.9% Test: 60.4% SUP resolution: Control: 60% Test: 100%	Bone level (mm) Control: Baseline: 3.9 ± 1.6 1 y: 2.2 ± 1.3 (0.001) Test: Baseline: 3.0 ± 0.9 1 y: 1.1 ± 0.8 (0.002) DF: Control: 1.6 ± 0.7 Test: 1.9 ± 1.3	NR	Surface characteristics may have an impact on the clinical outcome following surgical debridement, disinfection of the contaminated surfaces, and grafting with bovine-derived xenografts. Complete fill of the bony defect does not seem to be a predictable result.
Same as the 2011 study.	Same as the 2011 study	Same as the 2011 study	PD (mm): Baseline: TPS: 7.2 ± 1.5 SLA: 6.6 ± 1.3 7 y: TPS: 3.4 ± 0.6 SLA: 3.2 ± 0.7	BoP: Baseline: TPS: 90% ± 12.9% SLA: 75% ± 31.2% 7 y: TPS: 30% ± 19.7% SLA: 7.5% ± 12.1% PUS: Baseline: TPS: 70% SLA: 40% 7 y: TPS: 10% SLA: 0%	Bone level (mm): Baseline: TPS: 3.7 ± 1.6 SLA: 2.9 ± 0.9 7 y: TPS: 1.7 ± 0.9 SLA: 0.8 ± 1	7-y survival rate: TPS: 71.4% SLA: 83.3% Treatment success (no further BL, no PUS/BoP, PD < 6 mm): TPS: 14.3% SLA: 58.3%	Seven years after surgical treatment, patients in adequate supportive care maintained sufficient peri-implant conditions in many cases, particularly around SLA implants. Nevertheless, some patients required further treatment and some lost implants. The clinical decision on whether implants should be treated or removed should be based on several factors, including implant surface characteristics.

Appendix Table 1 *(cont)* **Characteristics of the Included Nonrandomized Studies in the Qualitative Analysis**

Author, study, design, and setting	No. of patients and implants	Follow-up time	Peri-implantitis definition	Peri-implantitis defect morphology (defect site characteristics)	Smoking status? (S, NS, FS)	History of periodontitis
Roccuzzo et al[70] (2020), private practice	14 patients, 14 implants TPS: 6 SLA: 8	10 y (follow-up study)	Same as the 2011 study	NR	3 S	Same as the 2011 study
Roos-Jansåker et al[77] (2007), university	12 patients, 16 implants	1 y	Progressive BL of ≥ 3 threads (1.8 mm) following the first year of healing + BoP and/or SUP	NR	8 S, 2 FS, 2 NS; 9% smokers after the implant surgery	Tooth loss due to periodontitis: 75%

BL = bone loss; BoP = bleeding on probing; CCT = controlled clinical trial; CHX = chlorhexidine; CTG = connective tissue graft; DBBM = deproteinized bovine bone mineral; DF = defect fill; dPTFE = dense polytetrafluoroethylene; EMD = enamel matrix derivative; FS = former smoker(s); KTW = keratinized tissue width; MBL = marginal bone level; mo = months; NR = not reported; S = smoker(s); NS = nonsmoker(s); PDR = pocket depth reduction; PPD = probing pocket depth; SUP = suppuration on probing; SLA = sandblasted acid etched; TPS = titanium plasma sprayed.

Decontamination method	Reconstructive approach	Regenerative materials	PD reduction, mean ± SD (n)	BoP and SUP reduction	MBL gain (mean ± SD)	Disease resolution or success criteria	Reported conclusion
Same as the 2011 study.	Same as the 2011 study	Same as the 2011 study	PD (mm): Baseline: TPS: 7 ± 1.4 SLA: 6.8 ± 1.4 10 y: TPS: 3.5 ± 0.5 SLA: 3.2 ± 0.5	BoP (%): Baseline: TPS: 92% ± 13% SLA: 75% ± 32.7% 10 y: TPS: 12.5% ± 21% SLA: 12.5% ± 19% SUP: Baseline: TPS: 30% SLA: 20% 10 y: TPS: 0% SLA: 0%	Bone level: Baseline: TPS: 3.4 ± 1.5 mm SLA: 3.1 ± 0.9 mm 10 y: TPS: 1.4 ± 0.1 mm SLA: 0.4 ± 0.6 mm	10 y: Survival rate: TPS: 55% SLA: 80% Treatment success (no further BL, no BoP/PUS, PD ≤ 5 mm): TPS: 29% SLA: 42%	The proposed reconstructive treatment followed by supportive care was able to maintain the majority of SLA implants in function, although the overall treatment success was limited and many implants were removed. Therefore, the decision to treat implants affected by peri-implantitis should be based on several factors, including surface characteristics.
Debridement: titanium curettes and hydrogen peroxide (3%) followed by saline rinse.	Submerged (abutments were placed back at 6 mo)	Alloplast + collagen membrane	PD (mm): Baseline: 5.1 ± 1.6 PDR (mm): 1 y: 4.2 ± 1.5 (2-7)	BoP: Baseline: 63.2% ± 23.0% (patient level), 81.2% (implant level) SUP: 93.8% (implant level)	BL: Baseline: 3.8 ± 1 mm Defect fill: 1 y: 2.3 ± 1.2 mm (0.6–5.1)	NR	Treatment of peri-implant defects using a bone graft substitute combined with an absorbable membrane and submerged healing results in defect fill and clinically healthier situations.

Appendix Table 2 Characteristics and Demographic Data in the Included RCTs

Publication, reference	No. of centers/ setting	Funding/ geographic location of study	Peri-implantitis definition	Restrictions to defect and site morphology for inclusion	Treatment arms	No. of patients and implants (n)	Mean age (mean ± SD)	Females (%)
Wohlfahrt et al[59,83†a] (2012/2014)	1 / university	Partial industry support / Europe	PPD ≥ 5 mm, BoP at 1+ implant site	Infrabony component of peri-implant defect (at least 4 mm). There were no other restrictions with regard to defect width or morphology.	Test: Porous titanium granules	16 patients, 16 implants	65 ± 10	56.25%
					Control: OFD alone	17 patients, 17 implants	57.2 ± 12.3	58.82%
Andersen et al[47†a] (2017)	1 / university	None / Europe	PPD ≥ 5 mm, BoP at 1+ implant site	Infrabony component of peri-implant infrabony component (at least 4 mm). There were no other restrictions with regard to defect width or morphology.	Test: Porous titanium granules	6 patients, 6 implants	67 ± 12.9	50%
					Control: OFD	6 patients, 6 implants	67.2 ± 11.8	75%
Aghazadeh et al[14†b] (2012)	1 / university	Full industry sponsorship / Europe	≥ 2 mm bone loss with PPD ≥ 5 mm with BoP/SUP (Lan et al 2011)	Must have at least 3-mm depth of angular peri-implant bone loss (radiograph) or a minimum of 1 implant with ≥ 2 mm bone loss with PPD ≥ 5 mm with BoP/SUP (Lan et al 2011).	Test: Autogenous bone	22 patients, 34 implants	70.1 ± 6.2	63.6%
					Control: Xenograft bone substitute	23 patients, 37 implants	67 ± 7.5	56.5%
Aghazadeh et al[45†b] (2022)	1 / university	Full industry sponsorship / Europe	≥ 2 mm bone loss with PPD ≥ 5 mm with BoP/SUP (Lan et al 2011)	Must have ≥ 3-mm depth of angular peri-implant bone loss (radiograph) or a minimum of 1 implant with ≥ 2 mm bone loss with PPD ≥ 5 mm with BoP/SUP (Lan et al 2011).	Test: Autogenous bone	16 patients, 25 implants	76.2 ± 7.6 [60 months]	NR
					Control: Xenograft bone substitute	23 patients, 38 implants	67.6 ± 7.3 [60 months]	NR
Heitz-Mayfield et al[50] (2023)	1 / university	Osteology Foundation / Australia	Clinical inflammation (BoP/SUP) with PD ≥ 5 mm, in addition to progressive bone loss	Contained (3- or 4-wall) infrabony defect that is ≥ 3 mm in depth (semi-circumferential or circumferential defects). The prosthesis had to have sufficient access for cleaning and proper probing. Only defects conducive to regeneration were included. "Uncontained defects" (ie, supracrestal bone defects, type 2, or implants outside the bony envelope, type Ia) were excluded. Implants with < 2 mm KTW were excluded.	Test: OFD + Xenograft	20 patients, 20 implants	54.5 ± 13.5	40%
					Control: OFD	20 patients, 20 implants	58.7 ± 9.6	60%

Smokers at the time of surgery (%)	Follow-up time (months)	Treated implant systems (no. of implants)	Detoxification and debridement method		Augmentation approach	
			Chemical decontamination	Mechanical decontamination	Applied bone graft substitute/filler	Sealing agent/ membrane
31.25%	12	Astra Tech (4), Nobel Biocare Mark III (9), Nobel Biocare Replace (1), Straumann (2)	3% H_2O_2 after suprastructure removal 24% EDTA gel	Area-specific titanium curettes	Porous titanium granules	None
52.94%	12	Astra Tech (5), Nobel Biocare Mark III (5), Nobel Biocare Replace (4), Straumann (2), Dentsply Frialit (1)	3% H_2O_2 after suprastructure removal 24% EDTA gel	Area-specific titanium curettes	None	None
0%	87.6	Branemark (Nobel Biocare), Astra Tech, Straumann	3% H_2O_2 after suprastructure removal 24% EDTA gel	Area-specific titanium curettes	Porous titanium granules	None
0%	87.6	Branemark (Nobel Biocare), Astra Tech, Straumann	3% H_2O_2 after suprastructure removal 24% EDTA gel	Area-specific titanium curettes	None	None
40.9%	12	Implamed (1), Nobel Biocare (17), Straumann (2), Ti-Unite (2), unknown (0)	3% H_2O_2	Titanium curettes	Autogenous bone	Bovine-derived collagen membrane
69.6%	12	Implamed (2), Nobel Biocare (17), Straumann (2), Ti-Unite (1), unknown (1)	3% H_2O_2	Titanium curettes	Xenograft (deproteinized bovine bone mineral) [BDX (Bio-Oss)]	Bovine-derived collagen membrane
NR	12, 36, 60	–	3% H_2O_2	Titanium curettes	Autogenous bone	Bovine-derived collagen membrane
NR	12, 36, 60	–	3% H_2O_2	Titanium curettes	Xenograft deproteinized bovine bone mineral	Bovine-derived collagen membrane
10%	12	Straumann (3), Nobel Biocare (14), other brands (3)	–	Titanium curettes, ultrasonic device with fine titanium tips	Xenograft deproteinized bovine bone mineral	Bilayer collagen membrane
10%	12	Straumann (7), Nobel Biocare (10), other brands (3)	–	Titanium curettes, ultrasonic device with fine titanium tips	–	–

Appendix Table 2 *(cont)* **Characteristics and Demographic Data in the Included RCTs**

Publication, reference	No. of centers/ setting	Funding/ geographic location of study	Peri-implantitis definition	Restrictions to defect and site morphology for inclusion	Treatment arms	No. of patients and implants (n)	Mean age (mean ± SD)	Females (%)
Monje et al[55] (2023)	1 / private practice	Support for biomaterials otherwise self-funded / Europe	As per 2017 World Workshop	Only defects conducive to regeneration were included. "Uncontained defects" (ie, supracrestal bone defects, type 2, or implants outside the bony envelope, type Ia) were excluded. Implants with < 2 mm KTW were excluded.	Test: Allograft bone substitute + collagen membrane	17 patients, 26 implants	64.7 ± 8.3	60%
					Control: Allograft bone substitute	18 patients, 25 implants	63.5 ± 10.6	64%
Jepsen et al[54] (2016)	5 / university	Industry support / Europe	Radiographic (PA) infrabony defect ≥ 3 mm, PD ≥ 5 mm, BoP/SUP	A radiographic infrabony defect ≥ 3 mm, PD ≥ 5 mm, BoP/SUP, intraoperative infrabony defect component ≥ 3 mm at the deepest site, 3 to 4 walls, defect with < 270 degree (circumferential), and a defect angle ≤ 35 degrees from the axis of the implant were needed.	Test: OFD + Porous titanium granules	33 patients, 33 implants	57.7 ± 12.6	51.5%
					Control: OFD	30 patients, 30 implants	59.1 ± 12.2	63.3%
Polymeri et al[56] (2020)	1 / university	Industry support / Europe	Marginal bone loss ≥ 3 mm radiographically, PD ≥ 5 mm, with BoP/SUP	Intraoperative: An infrabony defect component ≥ 3 mm at the deepest part and < 3 mm of osseous walls, marginal bone loss ≥ 3 mm radiographically, and a PD ≥ 5 mm with BoP/SUP were needed. Intraoperative: An infrabony defect component ≥ 3 mm at the deepest part and < 3 mm of osseous walls.	Test: Xenograft deproteinized bovine bone mineral (Bio-Oss)	11 patients, 11 implants	65.5 ± 11.2	5 (45%) M / 6 (55%) F
					Control: Xenograft granules (Endobon)	13 patients, 13 implants	57.3 ± 15.1	62%
Renvert et al[19†] (2018)	1 / university	Industry support / Europe	PD ≥ 5 mm, with BoP/SUP, peri-implant marginal bone loss in the form of a crater defect ≥ 3 mm assessed via radiographs	A peri-implant marginal bone loss in the form of a crater defect ≥ 3 mm assessed via radiographs were included. All treated defects were either 3- or 4-wall defects, had PD ≥ 5 mm, BoP/SUP, or peri-implant marginal bone loss in the form of a crater defect that was ≥ 3 mm assessed via radiographs.	Control: OFD	20 patients, 20 implants	70 ± 7.8	45%
					Test: OFD + alloplast bone substitute	21 patients, 21 implants	67.5 ± 11.3	62%

Smokers at the time of surgery (%)	Follow-up time (months)	Treated implant systems (no. of implants)	Detoxification and debridement method		Augmentation approach	
			Chemical decontamination	Mechanical decontamination	Applied bone graft substitute/filler	Sealing agent/ membrane
0%	6, 12	Anodized implants (7), acid-etched (10), titanium plasma sprayed (10), machined (0), unknown (4)	3% H_2O_2	Mini-five curettes, Gracey curettes, NiTi brush, implantoplasty	Allograft	Cross-linked collagen membrane
0%	6, 12	Anodized implants (18), acid-etched (4), titanium plasma sprayed (1), machined (1), unknown (0)	3% H_2O_2	Mini-five curettes, Gracey curettes, NiTi brush, implantoplasty	Allograft	–
33.3%	12	Ankylos (2), Astra OsseoSpeed (6), Dyna (1), Friadent Xive (1), Nobel Biocare (10), Straumann standard neck (5), TMI (3), Zimmer (4), Biomet 3i (1)	3% H_2O_2	Titanium curettes, titanium brush	Porous titanium granules	–
23.3%	12	Ankylos (1), Astra OsseoSpeed (4), Friadent Xive (2), Nobel Biocare (8), SIC Invent (1), Straumann standard neck (5), TMI (2), Zimmer (2), Biomet 3i (4)	3% H_2O_2	Titanium curettes, titanium brush	–	–
27%	6, 12	Biomet 3i (1/9%), Frialit (1/9%), MIS (1/9%), Nobel/Branemark (2/18%), Straumann (3/27%), ICX (1/9%), BioComp (1/9%), unknown (1/9%)	3% H_2O_2	Titanium curettes	Xenograft deproteinized bovine bone mineral	–
38%	6, 12	Astra (1/8%), BioHorizons (1/8%), Biomet 3i (3/23%), Nobel/Branemark (4/31%), Straumann (4/31%)	3% H_2O_2	Titanium curettes	Xenograft granules	–
25%	12	Branemark (11/ 55%), AstraTech (7/ 35%), unknown (2/ 10%)	3% H_2O_2	Titanium curettes	–	–
23.8%	12	Branemark (8/38.1%), AstraTech (9/42.9%), unknown (3/14.3%), Cresco (1/4.8%)	3% H_2O_2	Titanium curettes	Xenograft bovine-derived deproteinized hydroxyapatite ceramic	–

Appendix Table 2 *(cont)* **Characteristics and Demographic Data in the Included RCTs**

Publication, reference	No. of centers/ setting	Funding/ geographic location of study	Peri-implantitis definition	Restrictions to defect and site morphology for inclusion	Treatment arms	No. of patients and implants (n)	Mean age (mean ± SD)	Females (%)
Renvert et al[58†] (2021)	1 / university	Industry support with partial university support / Europe	PD ≥ 5 mm with BoP/SUP, peri-implant marginal bone loss in the form of an osseous defect/ crater defect ≥ 3 mm assessed via radiographs	Infrabony defect/ crater defect ≥ 3 mm assessed via radiographs. Verified infrabony component ≥ 3 mm during surgery and a defect circumference < 270 degrees, or a PD ≥ 5 mm with BoP/SUP were included.	Test: OFD + xenograft bone substitute + membrane	34 patients, 34 implants	62.2 ± 10.2	54%
				Peri-implant marginal bone loss in the form of an infrabony defect/ crater defect ≥ 3 mm assessed via radiographs, and verified infrabony component ≥ 3 mm during surgery as well as a defect circumference of < 270 degrees.	Control: OFD	32 patients, 32 implants	62.9 ± 13	50%
Isehed et al[51†c] (2016)	1 / university	Self-funded and university sponsored / Europe	PD ≥ 5 mm with BoP/SUP, peri-implant marginal bone loss in the form of an angular defect ≥ 3 mm assessed via radiographs	None/ PD ≥ 5 mm, BoP/SUP, peri-implant marginal bone loss in the form of an angular defect ≥ 3 mm assessed via radiographs were included.	Test: OFD + EMD	15 (3 dropped out) patients, 12 implants	70 (median age)	60%
					Control: OFD	14 (1 dropped out) patients, 13 implants	73.5 (median age)	64%
Isehed et al[52†c] (2018)	1 / university and private practice	Self-funded and university sponsored / Europe	PD ≥ 5 mm with BoP/SUP, peri-implant marginal bone loss in the form of an angular defect ≥ 3 mm assessed via radiographs	None/ PD ≥ 5 mm, BoP/SUP, peri-implant marginal bone loss in the form of an angular defect ≥ 3 mm assessed via radiographs were included.	Test: OFD + EMD	12 patients, 12 implants	NR	NR
					Control: OFD	14 patients, 14 implants	NR	NR
Isler et al[15†d] (2018)	1 / university	None / Turkey	Seventh and Eighth European Workshop on Periodontology: Peri-implant marginal bone loss ≥ 2 mm after delivery of final restoration, BoP/ SUP, with or without deepening PD	At least one implant demonstrating a 2-, 3- or 4-wall infrabony defect ≥ 3 mm. Seventh and Eighth European Workshop on Periodontology: Peri-implant marginal bone loss ≥ 2 mm after delivery of final restoration, with BoP/SUP with or without deepening PD. Defect for inclusion needs to have either a 2-, 3-, or 4-wall defect < 3 mm.	Test: CGF	26 patients, 26 implants	57.96 ± 9.07	38.5%
					Control: Collagen membrane	26 patients, 26 implants	56.15 ± 9.23	57.7%

Smokers at the time of surgery (%)	Follow-up time (months)	Treated implant systems (no. of implants)	Detoxification and debridement method		Augmentation approach	
			Chemical decontamination	Mechanical decontamination	Applied bone graft substitute/filler	Sealing agent/ membrane
23.52%	6, 9, 12	Modified surface (36/97%), nonmodified surface (1/3%)	3% H_2O_2	Titanium curettes, titanium brush	Xenograft deproteinized bovine bone mineral	Native bilayer collagen membrane
28.12%	6, 9, 12	Modified surface (32/94%), nonmodified surface (2/6%)	3% H_2O_2	Titanium curettes, titanium brush	–	–
26.7%	12	Nobel Turned (1/6.7%), Nobel TiUnite (0/0%), Astra (8/53.3%), Straumann SLA (5/33.3%), 3i (1/6.7%)	–	Ultrasonic device, titanium curettes, gauze, super floss, saline	0.3 mL EMD	–
42.9%	12	Nobel Turned (1/7.1%), Nobel TiUnite (5/35.7%), Astra (5/35.7%), Straumann SLA (3/21.4%), 3i (0/0%)	–	Ultrasonic device, titanium curettes, gauze, super floss, saline	–	–
9.2%, 12%	12, 36, 60	Nobel Turned (1/6.7%), Nobel TiUnite (0/0%), Astra (8/53.3%), Straumann SLA (5/33.3%), 3i (1/6.7%)	–	Ultrasonic device, titanium curettes, gauze, super floss, 0.3 mL EMD	0.3 mL EMD	–
25%, 31%	12, 36, 60	Nobel Turned (1/7.1%), Nobel TiUnite (5/35.7%), Astra (5/35.7%), Straumann SLA (3/21.4%), 3i (0/0%)	–	Ultrasonic device, titanium curettes, gauze, super floss	–	–
21%	6, 12	Modified (20/77%), nonmodified (6/23%)	–	Titanium curettes	Xenograft deproteinized bovine bone mineral	2 pieces of CGF
34.16%	6, 12	Modified (21/80.8%), nonmodified (5/19.2%)	–	Titanium curettes	Xenograft deproteinized bovine bone mineral	Native bilayer collagen membrane

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Appendix Table 2 *(cont)* **Characteristics and Demographic Data in the Included RCTs**

Publication, reference	No. of centers/ setting	Funding/ geographic location of study	Peri-implantitis definition	Restrictions to defect and site morphology for inclusion	Treatment arms	No. of patients and implants (n)	Mean age (mean ± SD)	Females (%)
Isler et al[53†d] (2022)	1 / university	None / Turkey	Seventh and Eighth European Workshop on Periodontology: Peri-implant marginal bone loss ≥ 2 mm after delivery of final restoration, BoP/ SUP, with or without deepening PD		Test: CGF	25 patients, 25 implants	57.88 ± 9.24	36%
					Control: Collagen membrane	26 patients, 26 implants	56.15 ± 9.23	57.7%
Regidor et al[57] (2023)	1 / private practice	Arrow Development S.L. and Geistlich / Europe	PPD ≥ 7 mm, BoP/ SUP and MBL ≥ 3 mm. In the absence of reference radiographs, a bone level ≥ 3 mm (Romandini et al 2021)	An intrabony defect ≥ 3 mm and ≤ 4 mm wide assessed via radiographs and confirmed intra-operatively. A minimum of 1 implant in function for < 1 year and a PPD ≥ 7 mm, (BoP/ SUP) and a marginal bone loss ≥ 3 mm were included. In the absence of reference radiographs, a bone level ≥ 3 mm was included (Romandini et al 2021).	Control: Access flap + xenograft bone substitute	22 (20 with dropouts) patients, 22 (20 with dropouts) implants	62.2 ± 10.2	63.6%
					Test: Access flap + xenograft bone substitute + collagen membrane	21 (19 with dropouts) patients, 21 (19 with dropouts) implants	60 ± 9	47.6%
Derks et al[48] (2022)	6 / NR	Osteology Foundation, grant / Europe	PPD ≥ 7 mm, BoP/SUP, and radiographically confirmed bone loss ≥ 3 mm. For cases lacking reference radiographs, bone levels ≥ 3 mm	A circumferential infrabony defect ≥ 3 mm deep. No minimum requirement for bony walls. Confirmed surgically. After ≥ 1 year of function, a PPD ≥ 7 mm, BoP/SUP, and radiographically confirmed bone loss ≥ 3 mm. For cases lacking reference radiographs, bone levels needed to be ≥ 3 mm.	Test: Access flap + xenograft bone substitute	69 patients, 73 implants	62.4 ± 11.3	59.4%
					Control: Access flap	69 patients, 74 implants	59.3 ± 11.5	68.1%
Emanuel et al[49] (2020)	1 / university	University / Israel	PPD of 6 to 10 mm, BoP with or without suppuration, and radiographic evidence for bone loss above 2 mm	Radiographic evidence of an intrabony defect ≥ 2 mm, a minimum of 2 mm of bone at implant apex, and < 2 mm distance to adjacent implant(s) were included.	Test: Access flap with alloplast bone substitute	14 patients, 18 implants	64.81 ± 7.61	59.3%
					Control: Access flap	13 patients, 14 implants	64.81 ± 7.61	59.3%

BoP = bleeding on probing; Cig/day = cigarettes per day; CGF = concentrated growth factors; EDTA = ethylenediaminetetraacetic acid; EMD = enamel matrix derivative; H_2O_2 = hydrogen peroxide; NR = not reported; OFD = open flap debridement therapy; PPD = probing pocket depth; SUP = suppuration.
[†]a–jArticles pertaining to the same study patient population.
All study designs were parallel-arm.

Smokers at the time of surgery (%)	Follow-up time (months)	Treated implant systems (no. of implants)	Detoxification and debridement method		Augmentation approach	
			Chemical decontamination	Mechanical decontamination	Applied bone graft substitute/filler	Sealing agent/ membrane
24%	12, 36	Modified (20/80%), nonmodified (5/19.2%)	–	Titanium curettes	Xenograft deproteinized bovine bone mineral	2 pieces of CGF
34.16%	12, 36	Modified (21/80.8%), nonmodified (5/19.2%)	–	Titanium curettes	Xenograft deproteinized bovine bone mineral	Native bilayer collagen membrane
4.5%	6, 12	Straumann (18), unclear (4)	–	Titanium curette, titanium brush at ≤ 1200 rpm	Xenogeneic bone substitute (Bio-Oss)	–
14.3%	6, 12	Straumann (13), Astra Tech (1), unclear (7)	–	Titanium curette, titanium brush at ≤ 1200 rpm	Xenogeneic bone substitute	Natural collagen membrane
23.2%	6, 12	Nobel Biocare (10), Astra Tech (35), Straumann (14), other (9), unclear (5)	–	Titanium curette, titanium brush (Nano NiTi Brush) at ≤ 1200 rpm	Xenograft deproteinized bovine bone mineral	–
30.4%	6, 12	Nobel Biocare (16), Astra Tech (28), Straumann (17), other (9), unclear (4)	–	Titanium curette, titanium brush at ≤ 1200 rpm	–	–
0%	6, 12	NR	–	Ultrasonic, sonic, or hand instruments and rinse with sterile saline	–	–
0%	6, 12	NR	–	Ultrasonic, sonic, or hand instruments and rinse with sterile saline	–	–

Appendix Table 3 Summary of the Primary Outcomes of the Included Randomized Controlled Trials

Publication, reference	Treatment arms	Follow-up time (months)	Intrasurgical assessment of defect morphology	Clinical outcomes		
				Mean PPD reduction, mean (SD/SE)	Mean BoP reduction, mean (SD/SE)	Mean SUP reduction, mean (SD/SE)
Wohlfahrt et al[†a] (2012)	Test: Porous titanium granules	12	2-wall: 3-wall / circumferential/3C/ circumferential + horizontal: 2 1- and 2-wall defects: 4 2- and 3-wall defects (1B & 3B): 7	1.7 (SD 1.7)	0.38 (SD 2.1)	NR
	Control: OFD	12	2-wall: 8 3-wall/ circumferential/3C/ circumferential + horizontal: 2 1- and 2-wall defects: 1 2- and 3-wall defects (1B & 3B): 5	2.0 (SD 2.3)	0.56 (SD 2.9)	NR
Andersen et al[†a] (2017)	Test: Porous titanium granules	12 ––––– 87.6	NR	NR	0.5	NR
	Control: OFD	12 ––––– 87.6	NR	NR	5 ––––– 4.6	NR
Aghazadeh et al[†b] (2012)	Test: Autogenous bone	12	NR	2.0 (SE 0.2)	44.8 (SE 6.3)	11.5 (SE 5.2)
	Control: Xenograft	12	NR	3.1 (SE 0.2)	50.4 (SE 5.3)	25.2 (SE 4.3)
Aghazadeh et al[†b] (2022)	Test: Autogenous bone	12, 36, 60	NR (12 M) NR (36 M) 3-wall/ circumferential/3C/ circumferential plus horizontal: 11' 4-wall defects / circumferential/1C: 3	NR 1.6 (SE 0.3) 1.7 (SE 0.4)	NR 50.7 55.6	NR
	Control: Xenograft	12, 36, 60	NR (12 M) NR (36 M) 3-wall/ circumferential/3C/ circumferential plus horizontal: 11 4-wall defects / circumferential/1C: 5	NR 3 (SE 0.3) 2.8 (SE 0.3)	NR 50.6 50.6	NR

Radiographic outcomes				
Mean Rx bone level gain	Implant failure/ extraction	Adverse events	Disease resolution/success criteria	Patient-reported outcomes
2.0 (SD 1.7)	NR	Perforation of implants through mucosa at 3 weeks (3) and at 6 months (6)	NR	NR
0.1 (SD 1.9)	NR	Perforation of implants through mucosa at 3 weeks (9) and at 6 months (13)	NR	NR
NR	0 ––––– 3	Four implants had a progression of bone loss at 12 months	NR	NR
NR	0 ––––– 0	Seven implants had a progression of bone loss at 12 months	NR	NR
0.2 (SE 0.3)	0	NR	PPD maximum 5 mm, no BoP, no SUP at any site, gain or no loss of bone: 11.1% PPD maximum 5 mm, maximum 1 BoP site per implant, no SUP at any site, gain or no loss of bone: 13.9%	NR
1.1 (SE 0.3)	0	NR	PPD maximum 5 mm, no BoP, no SUP at any site, gain or no loss of bone: 20.5% PPD maximum 5 mm, maximum 1 BoP site per implant, no SUP at any site, gain or no loss of bone: 38.5%	NR
NR -0.2 (SE 0.4) -0.7 (SE 1.5)	0	NR	NR NR No further evidence of bone loss from baseline to 5 y, no SUP, no PPD > 5 mm, and only one BoP site (from 4): 36%	NR
NR 1.6 (SE 0.3) 1.6 (SE 0.3)	0	NR	NR NR No further evidence of bone loss from baseline to 5 years, no SUP, no PPD > 5 mm, and only one BoP site (from 4): 78.3%	NR

Appendix Table 3 *(cont)* **Summary of the Primary Outcomes of the Included Randomized Controlled Trials**

Publication, reference	Treatment arms	Follow-up time (months)	Intrasurgical assessment of defect morphology	Clinical outcomes		
				Mean PPD reduction, mean (SD/SE)	Mean BoP reduction, mean (SD/SE)	Mean SUP reduction, mean (SD/SE)
Heitz-Mayfield et al (2023)	Control: OFD	12	3-wall/ circumferential/3C/ circumferential plus horizontal: 10 4-wall defects / circumferential/1C: 10 2- and 3-wall defects (1B & 3B): 10	3.275 Deepest PPD reduction: 7.6 (SD 1.6)	60%, 2.6 (SD 1.1)	46.3 (SD 32.7)
	Test: OFD + xenograft + bilayer collagen membrane	12	3-wall/ circumferential/3C/ circumferential plus horizontal: 12 4-wall defects / circumferential/1C: 8 2- and 3-wall defects (1B & 3B): 12	2.75 Deepest PPD reduction: 6.8 (SD 1.3)	70%, 2.8 (SD 1.1)	50 (SD 28.2)
Monje et al (2023)	Test: Xenograft and collagen membrane	6, 12	3-wall/ circumferential/3C/ circumferential plus horizontal: 3 4-wall defects / circumferential/1C: 8 2- and 3-wall defects (1B & 3B): 6 + 7	3.33 (SD 1.21) 3.41 (SD 1.15)	NR	NR
	Control: Xenograft	6, 12	3-wall/ circumferential/3C/ circumferential plus horizontal: 2 4-wall defects / circumferential/1C: 6 2- and 3-wall defects (1B & 3B): 9 + 7	4.13 (SD 1.45) 4.03 (SD 1.47)	NR	NR
Jepsen et al (2016)	Test: OFD+ porous titanium granules	12	NR	2.8 (SD 1.3)	56.1 (SD 30.5)	23.2 (SD 32.8)
	Control: OFD	12	NR	2.6 (SD 1.4)	44.9 (SD 38.2)	25.6 (SD 32.7)

Radiographic outcomes				
Mean Rx bone level gain	Implant failure/ extraction	Adverse events	Disease resolution/success criteria	Patient-reported outcomes
1 Deepest site: 1.7 (SD 1.6)	0	–	Heitz-Mayfield et al (2018): 18% Jepsen et al (2016): 11% Renvert et al (2018): 8% Derks et al (2022) & Regidor et al (2023): 9%	–
2.05 Deepest site: 2.4 (SD 1.4)	0	–	Heitz-Mayfield et al (2018): 17% Jepsen et al (2016): 12% Renvert et al (2018): 11% Derks et al (2022) & Regidor et al (2023): 10%	Higher VAS pain in test group and disturbance of daily activity
NR 1.72 (SD 0.72)	NR	NR	At 12 months: Absence of BoP or only one spot of nonprofuse BoP and/or SUP, PPD ≤ 5 mm, and no progressive bone loss: 75.1%	NR
NR 1.73 (SD 0.78)	NR	NR	At 12 months: Absence of BoP or only 1 spot of nonprofuse BOP and/or SUP, PPD ≤ 5 mm, no progressive bone loss: 79.2%	NR
3.515	NR	NR	PPD ≤ 4 mm, absence of BoP, no further bone loss: 30%	NR
0.9	NR	NR	PPD ≤ 4 mm, absence of BoP, no further bone loss: 23%	NR

Appendix Table 3 *(cont)* **Summary of the Primary Outcomes of the Included Randomized Controlled Trials**

Publication, reference	Treatment arms	Follow-up time (months)	Intrasurgical assessment of defect morphology	Clinical outcomes		
				Mean PPD reduction, mean (SD/SE)	Mean BoP reduction, mean (SD/SE)	Mean SUP reduction, mean (SD/SE)
Polymeri et al (2020)	Test: Xenograft	6, 12	NR	3.5 (SD 1.7) 3.6 (SD 1.7)	52.3 (SD 32.5) 54.5 (SD 33.2)	75 (SD 43.3) 79.5 (SD 40)
	Control: Xenograft	6, 12	NR	3.8 (SD 1.4) 3.8 (SD 1.4)	67.3 (SD 21.4) 50 (SD 10.2)	86.5 (SD 33.3) 84.6 (SD 33.1)
Renvert et al[†c] (2018)	Control: OFD	12	NR	2.5 (SE 0.31)	30	NR
	Test: OFD + xenograft (bovine derived deproteinized hydroxyapatite ceramic)	12	NR	3.6 (SE 0.2)	46	NR

Radiographic outcomes				
Mean Rx bone level gain	Implant failure/ extraction	Adverse events	Disease resolution/success criteria	Patient-reported outcomes
2 (SD 0.7) 2.2 (SD 0.8)	None	NR	PPD ≤ 5 mm, complete absence of BoP/SUP, and no further bone loss (Heitz-Mayfield, Needleman, Salvi, & Pjetursson [2014]; Jepsen et al [2019]): 2 from 11 (18%) Reduction of the radiographic defect ≥ 1 mm considered as treatment success (Renvert et al [2018]) for regenerative therapy: 100% PPD ≤ 5 mm, ≤ 1 site with BoP, absence of SUP, and no further bone loss (Renvert et al [2018]): 2 from 11 (18%)	NR
2.4 (SD 1) 2.8 (SD 1.3)	None	NR	PPD ≤ 5 mm, complete absence of BoP/SUP, and no further bone loss (Heitz-Mayfield, Needleman, Salvi, & Pjetursson [2014]; Jepsen et al [2019]): from 13 (0%) Reduction of the radiographic defect ≥ 1 mm considered as treatment success (Renvert et al [2018]) for regenerative therapy: 100% PPD ≤ 5 mm, ≤ 1 site with BoP, absence of SUP, and no further bone loss (Renvert et al [2018]): 1 from 13 (8%)	NR
0.2 (SD 0.6)	None	NR	Reduction of the radiographic defect ≥ 1 mm was considered as treatment success (Renvert et al [2018]) for regenerative therapy: 1 from 20 (5%)	NR
0.7 (SD 0.9)	None	NR	Reduction of the radiographic defect ≥ 1 mm was considered as treatment success (Renvert et al [2018]) for regenerative therapy: 9 from 21 (42.9%)	NR

Appendix Table 3 *(cont)* **Summary of the Primary Outcomes of the Included Randomized Controlled Trials**

Publication, reference	Treatment arms	Follow-up time (months)	Intrasurgical assessment of defect morphology	Clinical outcomes		
				Mean PPD reduction, mean (SD/SE)	Mean BoP reduction, mean (SD/SE)	Mean SUP reduction, mean (SD/SE)
Renvert et al[†c] (2021)	Test: OFD + xenograft + bilayer collagen membrane	6, 9, 12	3-wall/ circumferential/3C/ circumferential plus horizontal: 13 (35%) 4-wall defects / circumferential/1C: 24 (65%)	2.1 2 1.9 (SD 1.5)	NR NR 0.9 (SD 0.9)	NR NR 1.5 (SD 1.3)
	Control: OFD	6, 9, 12	3-wall/ circumferential/3C/ circumferential plus horizontal: 14 (41%) 4-wall defects / circumferential/1C: 20 (59%)	2.7 2.6 2.3 (SD 1.8)	NR NR 1 (SD 0.9)	NR NR 1.3 (SD 1.7)
Isehed et al[†d] (2016)	Test: OFD + EMD	12	Number of osseous walls from 2 to 4 (median 3)	2.8	23.3	51.70
	Control: OFD	12	Number of osseous walls from 2 to 4 (median 2)	3	15.7	35.21
Isehed et al[†d] (2018)	Test: OFD + EMD	12, 36, 60	NR	NR	26.6 13.3 37.7	1 (8.3%) 2 (20%) 0
	Control: OFD	12, 36, 60	NR	NR	16.5 23.2 45.7	1 (7.7%) 3 (33%) 0

Radiographic outcomes				
Mean Rx bone level gain	Implant failure/ extraction	Adverse events	Disease resolution/success criteria	Patient-reported outcomes
2.1 (SD 1.6)	2 implants lost	NR	No BoP (only 1 site with grade 1 BoP per 4 implant sites acceptable—1 dot of bleeding), no SUP, PPD ≤ 5 mm, and ≥ 1-mm defect fill: 32% RDF ≥ 0 mm, PPD at the implant ≤ 5 mm, no BoP, and no SUP at any of four assessed sites: 35%	Diary for first 8 days regarding the no. of ibuprofen tablets taken and postoperative pain on VAS. OHIP-14 at 6 weeks and 12 months. Final recall (12 months) assessed overall satisfaction.
3.6 (SD 2.3)	2 implants lost	NR	No BoP (only 1 site with grade 1 BoP per 4 implant sites acceptable—1 dot of bleeding), no SUP, PPD ≤ 5 mm, and ≥ 1-mm defect fill: 21% RDF ≥ 0 mm, PPD at the implant ≤ 5 mm, no BoP, and no SUP at any of four assessed sites: 30%	Diary for first 8 days regarding no. of ibuprofen tablets taken and postoperative pain on VAS. OHIP-14 at 6 weeks and 12 months. Final recall (12 months) assessed overall satisfaction.
0.9 mm	None	NR	NR	NR
Loss of 0.1 mm	1	NR	NR	NR
0.9 mm 1.2 mm 1.4 mm	0 0 2	NR	NR	NR
–0.1 0.8 1.3	1 2 1	NR	NR	NR

Appendix Table 3 *(cont)* **Summary of the Primary Outcomes of the Included Randomized Controlled Trials**

Publication, reference	Treatment arms	Follow-up time (months)	Intrasurgical assessment of defect morphology	Clinical outcomes		
				Mean PPD reduction, mean (SD/SE)	Mean BoP reduction, mean (SD/SE)	Mean SUP reduction, mean (SD/SE)
Isler et al[†e] (2018)	Test: Xenograft deproteinized bovine bone mineral + two pieces of concentrated growth factors	6, 12	2-wall: 11 (44%) 3-wall/ circumferential/3C/ circumferential plus horizontal: 5 (20%) 4-wall defects / circumferential/1C: 9 (36%)	2.98 2.2	76.93 61.54	NR
	Control: Xenograft deproteinized bovine bone mineral + porcine-derived bilayer collagen membrane (Bio-Gide)	6, 12	2-wall: 11 (42.3%) 3-wall/ circumferential/3C/ circumferential plus horizontal: 7 (26.92%) 4-wall defects / circumferential/1C: 8 (33.78%)	2.81 2.71	79.81 67.31	NR
Isler et al[†e] (2022)	Test: Xenograft deproteinized bovine bone mineral + two pieces of concentrated growth factors	12, 36	2-wall: 11 (44%) 3-wall/ circumferential/3C/ circumferential plus horizontal: 5 (20%) 4-wall defects / circumferential/1C: 9 (36%)	2.19 2.1	61.54 56.74	NR
	Control: Xenograft deproteinized bovine bone mineral + porcine-derived bilayer collagen membrane	12, 36	2-wall: 11 (42.3%) 3-wall/ circumferential/3C/ circumferential plus horizontal: 7 (26.92%) 4-wall defects / circumferential/1C: 8 (33.78%)	2.71 2.13	67.31 61.54	NR
Regidor et al (2023)	Test: Access flap + xenograft deproteinized bovine bone mineral	6, 12	10 (45.5%) contained, 12 (54.5%) 2- or 3-wall	NR 4.2 (SD 2.2)	NR 66.2 (SD 40)	NR 0.206
	Control: Access flap + xenograft deproteinized bovine bone mineral with natural collagen membrane	6, 12	4 (19%) contained, 17 (81%) 2- or 3-wall	NR 4.5 (SD 2.6)	NR 68.4 (SD 39.8)	NR 0.488

Radiographic outcomes				
Mean Rx bone level gain	Implant failure/ extraction	Adverse events	Disease resolution/success criteria	Patient-reported outcomes
NR 1.63 (1)	1 1	One implant was lost and it had SUP	NR According to Sanz & Chapple (2012) (referred to as success of therapy and disease resolution): No BoP/SUP, PPD < 5 mm, no further bone loss on radiographs after 12 months postoperative: 26.90%	NR
NR 1.98 (SD 0.75)	None	There was slight membrane exposure (without signs of inflammation) in the CM group for 3 implants (11.5%). It was managed with a CHX rinse and resolved.	NR According to Sanz & Chapple (2012) (referred to as success of therapy and disease resolution): No BoP/SUP, PPD < 5 mm, no further bone loss on radiographs after 12 months postoperative: 42.30%	NR
1.59 1.34	1 1	One implant had to be extracted due to concomitant SUP and increased PD (in the CGF group from 1 to 3 years). Also, two other implants had resurgical therapy (at 3 years).	Complete resolution of disease (without any BoP or SUP) at 3 years: 8 (30.7%)	NR
1.99 1.67	None	One implant had resurgical therapy at 3 years.	Complete resolution of disease (without any BoP or SUP) at 3 years: 9 (34.6%)	NR
NR 0.9 (SD 1.3)	None	Only in test group: 19% soft tissue dehiscence, membrane exposure (9.5%), and exposure of bone substitute (4.8%)	Implant not lost, BoP/SUP (–) at all sites, PPD ≤ 5 mm at all sites, and buccal MREC ≤ 1 mm: 0.45%	2 weeks: SSD higher pain in test group 12 months: overall satisfaction 85 in control group and 70 in test group. Esthetic satisfaction 80 in control group and 60 in test group.
NR 1.5 (SD 2.2)	None	Only in test group: 19% soft tissue dehiscence, membrane exposure (9.5%), and exposure of bone substitute (4.8%)	Implant not lost, BoP/SUP (–) at all sites, PPD ≤ 5 mm at all sites, and buccal MREC ≤ 1 mm: 0.36%	2 weeks: SSD higher pain in test group 12 months: overall satisfaction 85 in control group and 70 in test group. Esthetic satisfaction 80 in control group and 60 in test group.

Appendix Table 3 *(cont)* **Summary of the Primary Outcomes of the Included Randomized Controlled Trials**

Publication, reference	Treatment arms	Follow-up time (months)	Intrasurgical assessment of defect morphology	Clinical outcomes: Mean PPD reduction, mean (SD/SE)	Clinical outcomes: Mean BoP reduction, mean (SD/SE)	Clinical outcomes: Mean SUP reduction, mean (SD/SE)
Derks et al (2022)	Test: Access flap + xenograft bone substitute	6, 12	14 (19.2%) contained, 32 (43.8%) 3-wall, 27 (37%) 2-wall 14 (19.2%) contained, 32 (43.8%) 3-wall, 27 (37%) 2-wall	NR 3.7 (SD 2.1)	NR 44.8 (SD 36.6)	NR
	Control: Access flap	6, 12	22 (29.7%) contained, 22 (29.7%) 3-wall, 30 (40.5%) 2-wall	NR 3.7 (SD 2.3)	NR 49.6 (SD 41.1)	NR
Emanuel et al (2020)	Test: Access flap with alloplast bone substitute	6, 12	NR	1.59 (SD 1.22) 2.4 (SD 1.16)	0.196 0.363	NR
	Control: Access flap	6, 12	NR	1.33 (SD 1.54) 0.96 (SD 1.7)	0.13 0.152	NR

BoP = bleeding on probing; CM = collagen membrane; CGF = concentrated growth factors; EDTA = ethylenediaminetetraacetic acid; EMD = enamel matrix derivative; OFD = open flap debridement therapy; PPD = probing pocket depth; H_2O_2 = hydrogen peroxide; MREC = mucosal recession; NR = not reported; OHIP = Oral Health Impact Profile; Rx = radiographic; RDF = radiographic defect fill; SSD = statistically significant difference; SUP = suppuration; VAS = visual analog scale.
†a–j Articles pertaining to the same study patient population.

Appendix Table 4 Grading the Certainty of Evidence for Reconstructive Surgical Treatment of Peri-implantitis

Outcome variable	Location	Estimate (95% CI)	*P* value	Certainty assessment: Population (n)	Minimum follow-up (months)	Risk of bias	Inconsistency	Indirectness**	Imprecision	Other considerations	Certainty
PPD reduction	–	2.88 (2.49–3.28)	< .001	635 patients 687 implants	12	Moderate	Not serious*	Not serious	Not serious	None	High ★★★★
MBL gain	Allografts	1.14 (0.49, 1.78)	< .001	635 patients 687 implants	12	Moderate	Not serious*	Not serious	Serious	None	Moderate ★★★
BoP resolution	Initial BoP	1.025 (0.09, 1.95)	.03	501 patients 537 implants	12	Moderate	Not serious *	Not serious	Serious	None	Moderate ★★★
SUP resolution	Baseline SUP	0.575 (0.09, 0.91)	< .001	243 patients 265 implants	12	Moderate	Not serious *	Not serious	Serious	None	Low ★★

BoP = bleeding on probing; MBL = marginal bone level; PPD = probing pocket depth; Ref = reference; SUP = suppuration.
*All possible inconsistency controlled for using regression analysis.
**All included studies directly addressed the focused question (treatment of peri-implantitis using reconstructive approach).
Note that all study designs were RCTs.

Radiographic outcomes				
Mean Rx bone level gain	Implant failure/ extraction	Adverse events	Disease resolution/success criteria	Patient-reported outcomes
NR 1.1 (SD 1.4)	NR 1 (1.4%)	NR Implant loss: 1 (1.4%), No other events	Implant not lost, BoP/SUP (–) at all sites, PPD ≤ 5 mm at all sites, and buccal REC ≤ 1 mm: 61 (83.6%)	NR Overall satisfaction: 97.5 Esthetic: 95 Pain at 2 weeks: 10
NR 1.1 (SD 1)	NR 3 (4.1%)	NR Implant loss: 3 (4.1%), no other events	Implant not lost, BoP/SUP (–) at all sites, PPD ≤ 5 mm at all sites, and buccal MREC ≤ 1 mm: 64 (86.5%)	NR Overall satisfaction: 97.5 Esthetic: 95 Pain at 2 weeks: 10
1.08 (SD 1.25) 0.88 (SD 1.23)	None	None None	NR	NR
0.42 (SD 1.14) 0.33 (SD 1)	2 (14.3%) 2 (14.3%)	Implant loss (2, 14.3%) Implant loss (2, 14.3%)	NR	NR

Appendix Table 5 Summary of the Relevant Fixed-Effect Parameters of the Mixed-Regression Network Model for the Assessed Clinical Outcomes

Outcome	Estimate	95% CI [LB, UB]	*P* value
PPD reduction (mm)			
Baseline severity (initial depth mm)	0.62	[0.46, 0.77]	< .001
Baseline radiographic marginal bone loss (mm)	0.38	[0.14, 0.62]	.02
Allograft bone particulate (yes)	2.61	[1.66, 3.55]	< .001
Xenogeneic bone particulate (yes)	0.91	[0.62, 1.21]	< .001
Barrier membrane (yes)	0.19	[-0.06, 0.45]	.09
Adjunct use of titanium brushes (yes)	0.45	[0.15, 0.75]	< .01
Smoking (% individuals per treatment arm)	−0.02	[−0.03, −0.009]	< .01
Baseline KTW (mm)	0.65	[0.47, 0.83]	< .01
Time (months)	−0.019	[−0.03, −0.007]	< .01
Radiographic MBL gain (mm)			
Baseline defect morphology (% of circumferential defects)	0.04	[0.04, 0.04]	< .001
Allograft bone particulate (yes)	1.14	[0.49, 1.78]	< .001
Xenogeneic bone particulate (yes)	0.43	[0.11, 0.74]	.01
Barrier membrane (yes)	0.56	[0.22, 0.903]	< .001
Adjunct use of titanium brushes (yes)	0.12	[0.002, 0.255]	.03
Baseline KTW (mm)	0.32	[0.01, 0.64]	.03
Smoking (% individuals per treatment arm)	−0.01	[−0.01, −0.01]	< .001
Removal of implant suprastructures for surgical procedure (yes)	0.48	[0.13, 0.48]	.02
Primary wound closure and submerged healing approach (yes)	0.47	[0.12, 0.82]	.01
BoP reduction (%)			
Baseline severity (initial % BoP)	1.02	[0.09, 1.95]	.03
Removal of implant suprastructures for surgical procedure (yes)	6.65	[2.88, 10.42]	.01
SUP reduction (%)			
Baseline severity (%)	0.57	[0.37, 0.77]	< .001
Initial BoP (%)	2.99	[2.49, 3.49]	< .001
Mucosal recession (mm)			
Allograft bone particulate (yes)	−0.32	[−0.52, −0.11]	< .01
Xenogeneic bone particulate (yes)	−0.44	[−0.55, −0.33]	< .001
Baseline KTW (mm)	−0.12	[−0.23, −0.01]	.03

KTW = keratinized tissue width; BoP = bleeding on probing; SUP = suppuration; PPD = probing pocket depth; MBL = marginal bone level; CI = confidence interval.