The efficacy of bone reconstructive therapies in the management of peri-implantitis. A systematic review and meta-analysis

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The efficacy of bone reconstructive therapies in the management of peri-implantitis. A systematic review and meta-analysis

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Abstract

Aim: To evaluate the efficacy of bone reconstructive procedures for the reduction of probing pocket depth (PPD), bleeding on probing (BOP) and suppuration (SOP) in peri-implantitis-related bone defects at ≥ 12-month follow-up.

Materials and methods: Three databases were searched for RCTs and CCTs that compared bone reconstructive therapies to access flap surgery (Focused Question - FQ 1) and RCTs, CCTs and prospective case series that assessed the efficacy of reconstructive therapies (FQ 2). Meta-analysis was performed for FQ1 when ≥3 studies were identified, while for FQ2 a network was drawn based on RCTs with common treatment arms.

Results: Seven RCTs were identified for FQ1, while 5 RCTs and 6 prospective case series for FQ2. There was no significant difference in PPD change between access flap surgery and reconstructive surgery (-0.387; p=0.325) at 12 months. Furthermore, no clear differences in terms of PPD and BOP changes resulted from the different reconstructive therapies included in the network. Only a small percentage of treated cases with any modality achieved peri-implantitis resolution, as defined by different composite outcomes.

Conclusions: Reconstructive surgery does not offer significant improvements in peri-implant clinical parameters as compared to access flap surgery at 12-months. It was not possible to establish a hierarchy of efficacy amongst the different biomaterials employed for reconstructive surgery.

Clinical relevance

Scientific rationale for study: Owing to the high prevalence of peri-implantitis, there is a need to assess the efficacy of surgical reconstructive strategies, with the aim to develop evidence-based clinical guidelines.

Principal findings: Reconstructive surgery does not offer an added benefit in clinical parameters compared to access flap surgery at 12-months follow-up. A small percentage of cases achieve peri-implantitis resolution with both treatments.

Practical implications: Both access flap and reconstructive surgery can be applied for the treatment of peri-implant intrabony defects. However, disease relapse or lack of disease resolution should be expected, which may require additional surgical procedures or could lead to implant loss. Future studies are needed to assess aesthetic and patient-reported outcomes and to establish a hierarchy of efficacy amongst different biomaterials.

1. Introduction

It has been demonstrated in the literature that dental implants can achieve high long-term survival and success rates (94.6% and 89.7% after post-functional loading periods of 13.4 years and 15.7 years, respectively) (Moraschini et al., 2015, Albrektsson et al., 2012) and can be a valuable option for the rehabilitation of edentulous sites. However, a high prevalence of peri-implant diseases (peri-implant mucositis and peri-implantitis) has been documented in recent years (Lee et al., 2017, Meyle et al., 2019, Sousa et al., 2016), creating challenges for the application of predictable and effective treatment strategies in everyday clinical practice. Peri-implantitis is a biofilm-associated pathological condition occurring in tissues around dental implants, characterized by chronic inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone (Berglundh et al., 2018, Renvert et al., 2018a). The goal of peri-implantitis treatment is the resolution of soft tissue inflammation, the prevention of further marginal bone loss, and the long-term stability of the implant fixture. Several studies have shown that non-surgical therapy alone has limited efficacy in managing peri-implantitis, mainly due to the limited access to the implant surface, which makes it challenging to decontaminate the infected implant threads effectively (Faggion et al., 2014, Roccuzzo et al., 2018). Therefore, surgical access is often required after a pre-treatment phase comprising non-surgical debridement and re-assessment (Klinge et al., 2012, Heitz-Mayfield and Mombelli, 2014). Different surgical approaches, including non-reconstructive, reconstructive, and combined approaches appear to improve the outcomes of peri-implantitis treatment compared to non-surgical therapy alone (Schwarz et al., 2015, Khoury et al., 2019, Ramanauskaite et al., 2019).

Reconstructive therapy for the treatment of peri-implantitis is indicated in cases exhibiting intrabony defects with a minimum depth of 3 mm, three- or four-wall contained defects, and adequate keratinized mucosa (Jepsen et al., 2019).

While the goal of all surgical procedures is to resolve peri-implant inflammation, reconstructive therapies also aim to regenerate the bony defect, achieve re-osseointegration, and limit peri-implant soft-tissue recession (Jepsen et al., 2019).

A systematic review (Tomasi et al., 2019) investigating the available evidence on reconstructive therapies at peri-implantitis-related defects indicated that they are associated with larger improvements in marginal bone levels and defect fill compared with access flap

surgery, although no differences in terms of clinical measurements (reduction of probing depth and bleeding on probing) were found. A recent consensus report from the FDI World Dental Federation confirmed the same results and indicated that there is no evidence to support the superiority of a specific material, product or membrane in terms of long-term clinical benefits, thus making selection of reconstructive therapies empirical and subject to surgeon preference (Khoury et al., 2019). Nevertheless, in the 6th EAO consensus, reconstructive therapy for peri-implantitis was suggested to induce less soft-tissue recession when compared with access flap (Schwarz et al., 2021).

In light of new studies published in the past years, and in order to inform the development of evidence-based clinical guidelines, this systematic review aimed to provide updated evidence on the efficacy of reconstructive surgery compared with access flap surgery for the treatment of peri-implantitis. Moreover, considering the variety of bone substitutes, barriers and bioactive agents available in the market, we aimed to assess the efficacy of different reconstructive therapies and, if possible, establish a hierarchy between them.

2. Materials and methods

The aim of this review was to systematically evaluate the efficacy of different bone reconstructive procedures for the treatment of peri-implantitis-related bone defects.

The study protocol was registered in PROSPERO (CRD42022326652) before the beginning of the research and is in line with the Cochrane Handbook (Higgins JPT et al., 2022). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was adopted (Page et al., 2021).

2.1. Focused question 1 (FQ1)

In patients with peri-implantitis, what is the efficacy of different bone reconstructive therapies compared to access flap surgery in terms of pocket reduction and change in bleeding/suppuration on probing, at a minimum of 12-month of follow-up?

2.2. Focused question 2 (FQ2)

In patients with peri-implantitis, what is the long-term (≥12 months) performance of reconstructive therapies in terms of pocket reduction, change in bleeding on probing/suppuration?

2.3. Inclusion/exclusion criteria

The following inclusion criteria (based on the PICOS) were considered:

- Population – For both FQs: patients (both men and women) with or without history of periodontitis and affected by peri-implantitis. The definition of peri-implantitis should have been reported according to the criteria defined by the 2017 World Workshop (Berglundh et al., 2018, Renvert et al., 2018a) or with other well-defined criteria based on clear clinical and/or radiographic parameters reported in the selected studies. We excluded articles where uncontrolled (HbA1c>7) diabetic patients were included or where the level of control of diabetes could not be verified. Nevertheless, in those cases if authors provided separate data for non-diabetic patients, the study was still included and only data from non-diabetic patients were considered. For FQ 1 and 2, a minimum of 10 randomized/allocated patients per arm should have been reported by comparative studies (randomized controlled trials - RCTs and prospective controlled clinical trials - CCTs -), while for prospective case series (FQ2) a minimum of 30 patients should have been reported at the 12-month post-surgery follow-up.
- Intervention - For both FQs: reconstructive therapy of peri-implant bone defects employing bone substitutes/bone grafts/bone replacement grafts, barrier membranes according to the principle of Guided Bone Regeneration (GBR), bioactive agents, or combinations thereof. Bioactive agents included growth factors, autologous platelet concentrates and amelogenin (Donos, Dereka, & Calciolari, 2019).
- Comparison - For FQ1: non-reconstructive therapy of peri-implantitis employing access flap surgery. For FQ2: a different reconstructive therapy of peri-implantitis-related bone defects for RCTs and CCTs. For case series, where no control group was anticipated, only studies prospectively assessing reconstructive therapies of peri-implant bone defects were included.
- Outcome - Primary outcomes: Change in PPD, change in BOP/SOP; secondary outcomes: implant survival (defined as implant in place regardless of the state of the prosthesis or patient satisfaction), change in plaque scores, change in recession, radiographic marginal bone loss, radiographic bone defect fill, patient-reported outcome measures (including adverse events), risk of complications (e.g. membrane

exposure, infection, wound healing complications), combinations of outcomes/composite outcomes for resolution of peri-implantitis (e.g. absence of additional bone loss, absence of inflammation and shallow probing)

- Study design - For FQ1: RCTs, CCTs with a minimum follow-up of 12 months post-surgery. For FQ2: RCTs, CCTs and prospective case series with a minimum follow-up of 12 months post-surgery.

  In order to obtain the best level of evidence, only RCTs and CCTs were considered for FQ1. On the contrary, for FQ2 we extended the inclusion to prospective case series to account for the limited number of RCTs/CCTs and to overall assess the efficacy of reconstructive surgery. However, for FQ2 case series were only qualitatively presented, while RCTs/CCTs were selected with the aim to perform a network meta-analysis, if possible. For both FQs, split mouth studies were included but considered separately from parallel-designed studies. Case reports, review papers, conference abstracts and opinion articles were excluded.

2.4. Search methods for study identification

A sensitive strategy was developed aiming to identify all RCTs, CCTs and case series (for PICOS 2) meeting the inclusion/exclusion criteria (Supplementary Material, Appendix 1).

The research strategy included terms related to the Population and the Intervention/Comparison investigated in this review, which were combined with the boolean operator "AND". Three main databases were searched, MEDLINE via OVID, EMBASE and The Cochrane Database [including the Central Register of Controlled Trials (CENTRAL)], updated to April 2022. A literature search update was performed on 1st October 2022 to identify any new relevant article. Limitation to human studies was achieved using the double negation strategy suggested by the Cochrane handbook, i.e. combining the results with NOT (exp animals/ not humans.sh.). Bibliographies of review articles on this topic and of all studies included for data extraction were screened and the database Web of Science was used to identify all the papers that cited the included papers. Any ambiguous or incomplete data were researched further by contacting the authors responsible for the work.

In an attempt to include both published and unpublished data, a specific theses database, www.theses.com/ was searched and a hand search was performed for the last 2

years for journals relevant to this topic (Journal of Clinical Periodontology, Clinical Oral Implants Research, Journal of Periodontology, Journal of Dental Research, Journal of Clinical Investigation, Clinical Implant Dentistry and Related Research). Grey literature was investigated in a dedicated database (https://easy.dans.knaw.nl/ui/datasets/id/easy-dataset:200362) and clinicatrials.gov was searched to identify potential ongoing or already completed RCTs/CCTs meeting the inclusion and exclusion criteria. Whenever the identified studies were not already published, authors were contacted to enquire about the stage of the study. We included studies that were still unpublished at the time this review was performed, as long as the authors were willing to provide detailed information on the protocol, data collection and statistical analysis performed.

No language restrictions were applied to minimize the risk of language bias.

2.5. Methods for study selection and data extraction

A two-stage screening (titles and abstract first, followed by full-text) was carried out in duplicate and independently by two reviewers (EC and VS). Any disagreement was resolved by discussion and if necessary, a third reviewer (ND) was consulted. Calculation and presentation of the level of agreement at each of the two-stage screening was be carried out by using Kappa statistics.

At the second stage, a data screening and abstraction form was devised to verify the study eligibility, carry out the methodological quality assessment and extract data on study characteristics and outcomes for the included studies.

Data extraction was performed independently and in duplicate by two reviewers (EC, MG). In case of missing or unclear information, the authors of the included reports were contacted by email to provide clarification or missing information. Whenever numerical data were not presented, WebPlotDigitizer was employed to extrapolate the raw data, as suggested by the Cochrane Handbook (Li et al., 2022). In case of missing or incomplete data and absence of further clarification by study authors the report was excluded from the analysis.

Multiple reports generated from the same study were collated, so that each study, rather than each report, was the unit of interest in the review, as indicated in the Cochrane Handbook (Higgins JPT et al., 2022).

2.6. Assessment of risk of bias in included studies

Quality assessment was conducted independently by one experienced reviewer (EC), as part of the data extraction process. As per the Cochrane Handbook, the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) can be applied to all "follow-up" studies, a term that identifies a category of studies in which "participants are followed up from the start of intervention up to a later time for ascertainment of outcomes of interest" (Sterne et al., 2016). As such, ROBINS-I was employed for CCTs and case series, while the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (updated October 2018) was employed for RCTs (https://sites.google.com/site/riskofbiastool/welcome/home/current-version-of-robins-i?authuser=0).

2.7. Data synthesis

Regarding FQ1, meta-analysis was performed whenever ≥3 studies with similar characteristics were identified.

For the primary outcomes the mean difference between the values at x months of follow up and at baseline (Δ(x months – basal)), along with its standard deviation, was extrapolated from each study. When the standard deviation (SD_Δ) of Δ was not available, but a p-value was reported in the paper, the correspondent *t* statistics (with *n*-1 degrees of freedom, where *n* was the sample size) was calculated and the formula: $SD = \frac{\Delta * \sqrt{n}}{t_{n-1}}$ was used. When the p value was not reported and/or was not a punctual value (e.g. <0.01), the SD was estimated according to the formula: $SD^2_\Delta = SD^2_{x\ months} + SD^2_{baseline} - 2r * SD_{x\ months} * SD_{baseline}$, where $SD_{x\ months}$ and $SD_{baseline}$ were the standard deviations of the outcome at x months of follow up and at baseline, respectively, and r was the Pearson's correlation coefficient between the observations at the two times, that we assumed to be equal to 0.5 (Chow et al., 2003).

The primary endpoint (PE) considered was the difference between the mean change Δ(x months – basal) for access flap surgery and for reconstructive surgery ($PE_{x\ months} = \Delta_{access\ flap}$(x months – basal) - $\Delta_{reconstructive}$(x months – basal)). For each study, the point estimate of PE was obtained as the difference of the estimated mean changes in the two arms. The standard error (SE) was calculated from the standard deviations SD^2_Δ in the two arms, accounting for the number of patients and assuming independence between groups:

$$SE_{PE}=\sqrt{\frac{SD^2_{\Delta\,\text{access flap}}}{n_{\text{access flap}}}+\frac{SD^2_{\Delta\,\text{reconstructive}}}{n_{\text{reconstructive}}}}.$$

The forest plot of the study-specific results was drawn. According to the heterogeneity between the studies, a fixed-effects or random-effects model was used to combine the study-specific estimates of the primary endpoint, accounting for possible between-study heterogeneity (we adopted the DerSimonian and Laird approach). The 95% prediction interval of the overall effect was also calculated, which is the interval where the true effect is expected to lie in 95% of similar studies that might be performed in the future (IntHout et al., 2016). Heterogeneity was quantified in terms of I^2 statistic, i.e. the percentage of total variability attributable to discrepancies among studies. Whenever studies included more than one implant per patient, separate meta-analyses including and excluding these studies were performed.

The same approach was followed to perform meta-analysis of secondary outcomes, whenever applicable.

For FQ2, in case a common network of treatments was clearly identifiable (i.e. more than 2 treatment modalities were compared in different RCTs or CCTs, so that each study involved had at least one common arm with another study), a network meta-analysis was performed. In case the amount of information was scarce (e.g. only one study for each comparison in the network), the effect estimates for the direct comparisons were reported, and the effect estimates for the indirect comparisons calculated, but no ranking of treatments was produced.

All the statistical analyses were performed using Stata 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

2.1. Assessment of reporting biases

Publication bias was assessed by testing for funnel plot asymmetry, as described in the *Cochrane Handbook (Higgins JPT et al., 2022)*. If asymmetry was evident, it was investigated and the possible causes described. Egger's test for small-study effects was also performed.

3. Results

A total of 6282 unique records were identified and screened for title and abstract, which led to 104 articles eligible for full-text screening (Figure 1). Twenty-six articles eventually met the inclusion/exclusion criteria and were included in the qualitative analysis (reasons for exclusion are reported in the Supplementary Material, Appendix 2). A high level of agreement was found between the reviewers during both stages of the screening process ($K > 0.98$). Articles describing different follow-ups or outcomes from the same clinical trial were grouped together, thus resulting in a total of 18 original trials, including 12 RCTs (17 articles) (Renvert et al., 2021, Wohlfahrt et al., 2012, Jepsen et al., 2016, Andersen et al., 2017, Isler et al., 2018, Emanuel et al., 2020, Polymeri et al., 2020, Rakasevic and Gabric, 2021, Derks et al., 2022, Isler et al., 2022, Regidor et al., 2022, Isehed et al., 2018, Isehed et al., 2016, Renvert et al., 2018b, Aghazadeh et al., 2020, Aghazadeh et al., 2012, Aghazadeh et al., 2022), 1 CCT (3 articles) (Roos-Jansåker et al., 2014, Roos-Jansaker et al., 2011, Roos-Jansaker et al., 2007) and 5 prospective case series (6 articles) (Roccuzzo et al., 2021, Mercado et al., 2018, Froum et al., 2015, Roccuzzo et al., 2016, La Monaca et al., 2018, Gonzalez Regueiro et al., 2021). At the time this review was written, 1 RCT was under peer review (Regidor et al., 2022) and another was published as part of a book chapter (Rakasevic and Gabric, 2021) [with baseline and 3-month data already published (Rakasevic et al., 2016)]. Both studies were identified through clinicaltrials.gov and their data were obtained upon contacting the authors. The main characteristics of the included studies are summarized in Table 1. Briefly, 5 studies took place in a private practice/specialist clinic (Renvert et al., 2018b, Aghazadeh et al., 2022, Aghazadeh et al., 2020, Aghazadeh et al., 2012, Froum et al., 2015, Regidor et al., 2022, Roccuzzo et al., 2021, Roccuzzo et al., 2016), 3 in a mixed setting of university and private practice (Renvert et al., 2021, Derks et al., 2022, Roos-Jansåker et al., 2014, Roos-Jansaker et al., 2011, Roos-Jansaker et al., 2007) and the remaining studies in university/hospital. Apart from three studies that only mentioned that active/untreated periodontitis was an exclusion criterion (Emanuel et al., 2020, Gonzalez Regueiro et al., 2021, Regidor et al., 2022), all the remaining studies either directly mentioned that a percentage of participants had a history of periodontitis or indicated that periodontal treatment was performed prior to the peri-implantitis surgery.

Only two studies specifically referred to the EFP definition of peri-implantitis (Gonzalez Regueiro et al., 2021, Isler et al., 2022, Isler et al., 2018). However, most of the remaining

studies referred to a combination of clinical and radiographic features in line with the recommendations by the EFP (≥3mm radiographic bone loss and/or PPD≥6mm in conjunction with bleeding on probing (Renvert et al., 2018a)) (Table 1).

The surgical implant decontamination protocols applied were heterogeneous, ranging for instance from applying ultrasonic, sonic or hand instruments and rinsing of the implants with sterile saline (Emanuel et al., 2020) or EDTA (Mercado et al., 2018), to the use of titanium curettes and titanium brushes (Derks et al., 2022, Regidor et al., 2022). The adjunctive antibiotic regime used in conjunction with surgery also varied considerably in the included studies (Table 2 and 3). The great majority employed systemic antibiotics, but the type, dosage and duration of treatment (from 5 to 10 days) differed amongst the studies. In 3 studies, local antibiotics were employed (Gonzalez Regueiro et al., 2021, Mercado et al., 2018, Emanuel et al., 2020).

3.1. Risk of bias

When focusing on RCTs included in FQ1, 4 raised some concerns in one domain (predominantly due to bias in measurement of the outcome) (Renvert et al., 2018b, Renvert et al., 2021, Jepsen et al., 2016, Derks et al., 2022), while 3 studies were considered at high risk of bias, mainly due to the combination of missing outcomes and bias in selection of the reported results (Andersen et al., 2017, Wohlfahrt et al., 2012, Emanuel et al., 2020, Isehed et al., 2018, Isehed et al., 2016) (Figure 2 and Supplementary Material, Appendix 15). Amongst the RCTs included in FQ2, 2 were at high risk (Regidor et al., 2022, Rakasevic and Gabric, 2021), two raised some concerns (Aghazadeh et al., 2020, Aghazadeh et al., 2012, Aghazadeh et al., 2022, Polymeri et al., 2020) and one was at low risk of bias (Isler et al., 2022, Isler et al., 2018) (Figure 3 and Supplementary Material, Appendix 16). In particular, the domains related to the randomization process raised some concerns in 60% of the studies, while the domains related to missing outcomes and selection of the reported results raised concerns in 40% of the studies.

Moreover, amongst the studies fulfilling FQ2, 1 CCT (Roos-Jansåker et al., 2014, Roos-Jansaker et al., 2011, Roos-Jansaker et al., 2007) was at serious risk of bias 3 prospective cohort studies (Gonzalez Regueiro et al., 2021, La Monaca et al., 2018, Mercado et al., 2018) were considered at serious risk of bias and 2 prospective cohort studies (Froum et al., 2015, Roccuzzo et al., 2021, Roccuzzo et al., 2016) at critical risk of bias. Most of the biases noted originated from

the domain related to measurement of the outcome or the presence of confounding (Figure 4 and Supplementary material, Appendix 17). The fact that we included one study under peer review (Regidor et al., 2022) and one study whose data were only partially published in a book chapter (Rakasevic and Gabric, 2021) contributed to increased sources of bias.

3.2. Efficacy of reconstructive surgery vs. access flap surgery (FQ1)

- Study characteristics and primary outcomes

Seven RCTs (9 articles) (Renvert et al., 2021, Wohlfahrt et al., 2012, Jepsen et al., 2016, Andersen et al., 2017, Emanuel et al., 2020, Isehed et al., 2018, Isehed et al., 2016, Renvert et al., 2018b, Derks et al., 2022) assessed the efficacy of reconstructive surgery (total of 200 implants in 194 patients) compared to access flap surgery (total of 188 implants in 184 patients). Different types of reconstructive surgeries were documented, including the use of titanium granules (Andersen et al., 2017, Wohlfahrt et al., 2012, Jepsen et al., 2016), amelogenin (Isehed et al., 2018, Isehed et al., 2016), deproteinized bovine bone mineral (DBBM or DBBM graft with 10% collagen) alone (Renvert et al., 2018b, Derks et al., 2022) or combined with a native bilayer collagen membrane (Renvert et al., 2021), or a beta-tricalcium phosphate graft formulated with prolonged release local doxycycline (Emanuel et al., 2020) (Table 2). Three RCTs reported that periodontal treatment was completed before the study without specifically mentioning non-surgical treatment (NST) of the implant (Andersen et al., 2017, Wohlfahrt et al., 2012, Isehed et al., 2018, Isehed et al., 2016, Renvert et al., 2018b), one study failed to provide any information on this respect (Emanuel et al., 2020), whereas the remaining 3 studies indicated that implant NST was performed prior peri-implantitis surgical treatment (Renvert et al., 2021, Jepsen et al., 2016, Derks et al., 2022) (Table 1).

The type of peri-implant intrabony defects considered in the included studies varied with respect to number of walls and configuration (Table 2), as well as the healing protocol, with 4 studies reporting unsubmerged healing (Derks et al., 2022, Jepsen et al., 2016, Renvert et al., 2021, Isehed et al., 2018, Isehed et al., 2016), one reporting submerged healing (Andersen et al., 2017, Wohlfahrt et al., 2012) and the others not providing clear information (Emanuel et al., 2020, Renvert et al., 2018b). Implant decontamination during surgery was also performed according to different protocols (details in Table 2), but none of the studies performed implantoplasty.

Meta-analysis could be performed (FQ1) only for PPD changes between baseline and 12 months of follow-up. Considering the heterogeneity of the reconstructive therapies employed, meta-analysis was performed only for studies employing a bone graft associated or not with a barrier (4 studies (Emanuel et al., 2020, Renvert et al., 2018b, Renvert et al., 2021, Derks et al., 2022)), while studies employing titanium granules (Andersen et al., 2017, Wohlfahrt et al., 2012, Jepsen et al., 2016) or bioactive factors alone (Isehed et al., 2018, Isehed et al., 2016) were not included. The estimated mean difference between access flap surgery and reconstructive surgery was -0.387 (95% CI -1.157, 0.384; p=0.325) (Figure 5). The 95% prediction interval of the overall effect for PPD ranged from -2.75 mm to 1.97 mm. I^2 was 66.4%, thus indicating moderate between-study heterogeneity (hence the choice of a random-effects model). The funnel plot (Appendix 3) did not show evidence of small-study effects, which was also confirmed by the Egger's test (p=0.617), although the small number of included studies does not allow to make robust conclusions. Since all studies but one (Derks et al., 2022) included one implant per patient, we also performed a second meta-analysis excluding this study (which reported only an implant-level analysis), but a similar outcome was obtained (Supplementary Material, Appendix 4). It is also important to highlight that out of the studies included in the meta-analysis, 2 considered PPD at the deepest site of the involved implants (Derks et al., 2022, Emanuel et al., 2020), while 2 considered the average PPD around the treated implants (Renvert et al., 2021, Renvert et al., 2018b).

None of the studies included in the meta-analysis was at low risk of bias, but 3 presented some concerns (Renvert et al., 2021, Renvert et al., 2018b, Derks et al., 2022) and one was at high risk of bias (Emanuel et al., 2020) (Figure 2).

A separate meta-analysis including all types of reconstructive therapies is presented in the Supplementary Material (Appendix 5)

Amongst the 5 studies that reported on BOP changes, 4 did not show differences between the two surgical approaches (Renvert et al., 2018b, Derks et al., 2022, Jepsen et al., 2016, Isehed et al., 2016), while Emanuel et al. (Emanuel et al., 2020) indicated a statistically significant difference between reconstructive therapy and access flap surgery when data were analyzed with the implant as the statistical unit and when all implant sites were averaged (BOP change at 12 months of 36.3% and 15.2%, for reconstructive and access flap surgery, respectively) or when the subject was the statistical unit and all implant sites were averaged (BOP change at 12 months of 45.2% and 18.6%%, for reconstructive and access flap

surgery, respectively). Remarkably, Isehed et al. (Isehed et al., 2016) indicated that while in both groups there was a significant BOP reduction after surgery, at 12 months there was a relapse (to a BOP score of approximately 70%) in both groups. No differences were also indicated in relation to the change in SOP at the peri-implantitis-involved implants according to the surgical approach applied (Derks et al., 2022, Jepsen et al., 2016, Isehed et al., 2016).

- Secondary outcomes

Clinical outcomes

According to Derks et al (Derks et al., 2022), buccal recession was less pronounced after reconstructive surgery with DBBM graft with 10% collagen, compared to access flap surgery (0.7 mm vs. 1.1 mm) at 12 months, but this outcome was not confirmed by three other studies using an alloplastic graft or DBBM alone or combined with a collagen membrane (Renvert et al., 2021, Emanuel et al., 2020, Renvert et al., 2018b). Moreover, while Derks et al (Derks et al., 2022) reported less pronounced gain in keratinized tissue width at 12 months (0.1 vs. 0.5 mm) using reconstructive surgery, another study with a follow-up of 7 years suggested an opposite trend (Andersen et al., 2017).

Implant survival and composite outcomes

Limited data could be extrapolated in terms of implant loss and implant survival following treatment of peri-implantitis. Nevertheless, at 12 months, implant survival was similar between the two treatment procedures, ranging from 85.7% to 100% for access flap and from 95% to 100% for reconstructive therapy. Only 2 studies had a longer follow up. Although only 17 out of the original 32 patients were enrolled for the 7-year study by Andersen et al. (Andersen et al., 2017), the authors suggested unpredictable long-term survival for peri-implantitis defects treated with porous titanium granules (3 implant lost in this group and none in the AFS group). In a 5-year follow-up study, the survival rate was 85% (11 out 13 implants) for implants that underwent reconstructive therapy with DBBM as compared to 75% (9 out of 12 implants) for implants that underwent AFS (Isehed et al., 2018).

Different composite outcomes were considered to evaluate peri-implantitis resolution (see Supplementary Material), but the majority of the studies did not suggest a significant difference between the two treatment approaches (Renvert et al., 2021, Derks et al., 2022, Jepsen et al., 2016). Only one study indicated that when considering success as defect fill ≥1.0

mm, with PPD values at the implants ≤5 mm, no BOP (one out of four sites per implant with BOP grade 1 accepted), and no suppuration (at any of four assessed sites per implant), the number needed to treat analysis identified an absolute risk reduction of 32.8% in favour of the reconstructive procedure (Renvert et al., 2018b).

Radiographic outcomes

A meta-analysis for changes in radiographic mean bone levels included was performed by combining the 4 studies (Emanuel et al., 2020, Renvert et al., 2018b, Renvert et al., 2021, Derks et al., 2022) reporting on bone grafts associated or not with barriers and it showed a statistically significant difference between access flap surgery and reconstructive surgery of -0.75 mm (95%CI -1.391, -0.109; p=0.022) (Figure 6). The 95% prediction interval ranged from -2.90 mm to 1.40 mm. I^2 was 83.4%, thus indicating a high level of between-study heterogeneity. The asymmetric funnel plot (Supplementary Material, Appendix 6) showed a slight asymmetry, confirmed also by the Egger's test (p-value of Egger's test = 0.068). However, this result should be considered as weak, since the meta-analysis included only 4 studies. A separate meta-analysis excluding the study that considered >1 implant per patient (Derks et al., 2022) and another meta-analysis including all 7 identified studies reporting on reconstructive therapies is reported in Supplementary Material (Appendix 7 and 8) and gave similar results.

PROMs and adverse events/complications

A similar number of adverse events and complications was associated with reconstructive and AFS therapy (Appendix 14). Only two studies considered PROMs (Appendix 11), with no significant differences in terms of pain scores, number of tablets taken and satisfaction (Renvert et al., 2021, Derks et al., 2022).

Additional details on secondary outcomes can be found in Supplementary Material (Appendix 11, 12, 13, 14, 18).

3.3. Efficacy of different reconstructive approaches (FQ2)

- Study characteristics and primary outcomes

Five RCTs (8 articles)(Isler et al., 2022, Isler et al., 2018, Regidor et al., 2022, Polymeri et al., 2020, Rakasevic and Gabric, 2021, Aghazadeh et al., 2020, Aghazadeh et al., 2012, Aghazadeh et al., 2022) and 6 prospective case series (9 articles)(Mercado et al., 2018, La Monaca et al., 2018, Gonzalez Regueiro et al., 2021, Roccuzzo et al., 2021, Roccuzzo et al., 2016, Froum et al., 2015, Roos-Jansåker et al., 2014, Roos-Jansaker et al., 2011, Roos-Jansaker et al., 2007) assessed the efficacy of reconstructive peri-implantitis therapy. Traditional meta-analysis could not be performed due to the heterogeneity of the reconstructive therapies performed, which included different types of graft (autograft, DBBM, allograft or hydroxyapatite bone substitute) alone or combined with different types of resorbable membranes (collagen-based, concentrated growth factor-based) and/or bioactive factors (enamel matrix derivative) or local antibiotics (doxycycline, piperacillin/tazobact) (Table 3).

In one study, bone reconstructive therapy was also associated with soft tissue augmentation with a subepithelial connective tissue graft when keratinized tissue was <2 mm (Froum et al., 2015). The heterogeneity between studies related also to the implant decontamination protocol applied (details in Table 3), type of healing (submerged vs. unsubmerged) and on the performance or not of implantoplasty (details reported in Table 3). A part from 3 studies where they reported that periodontal treatment was performed prior to surgery but they did not specify if this included also debridement of the implant (Roos-Jansaker et al., 2007, Froum et al., 2015), in the other studies NST was provided to the implants.

Regardless of the biomaterials applied, reconstructive therapy led to a mean PPD reduction ranging from 2 to 4.5 mm and to a mean reduction in BOP ranging from 44.8% to 86% at 12 months post therapy (more details in Supplementary Material, Appendix 9). Only few studies reported on SOP, but they all confirmed a significant reduction in the peri-implantitis-treated implants at 12 months (Polymeri et al., 2020, Regidor et al., 2022, Roccuzzo et al., 2016, Aghazadeh et al., 2012, Roos-Jansaker et al., 2007) and 5 years (Roccuzzo et al., 2021) post-surgery.

While 1 RCT considered the same reconstructive therapy in both treatment arms (DBBM and native collagen membrane) (Rakasevic and Gabric, 2021) and therefore could not be included, for the remaining four RCTs (Polymeri et al., 2020, Regidor et al., 2022, Isler et al., 2018, Aghazadeh et al., 2012) we developed a network for PPD and BOP changes at 12 months post-surgery based on the assumption that DBBM and DBBM with 10% collagen would behave similarly and that different types of collagen membranes (Bio-gide, Geistlich, Wolhusen,

Switzerland and OsseGuard, ZimVie, Westminster, Colorado) would behave similarly. Overall, we did not find any relevant difference between the treatments included in the network, apart from an improved PPD reduction when a xenogenic rather than an autologous graft was applied in combination with a collagen membrane, but this was based on the outcomes of one single study (Aghazadeh et al., 2012) (Figure 7). We estimated that adding a resorbable collagen membrane (either native or cross-linked) to DBBM/DBBM with 10% collagen would lead to a non-significant mean difference in PPD reduction of 0.3 mm (95% CI -1.21mm, 1.81mm; p=0.698) and to a non-significant mean difference in BOP of 2.2% (95%CI -22.8%, 27.2%; p=0.865) (Regidor et al., 2022) (Figure 7). No significant differences were also suggested when performing reconstructive therapy with different types of xenografts (Polymeri et al., 2020) and when combining a native collagen membrane instead of a concentrated growth factor membrane to DBBM/DBBM with 10% collagen (Isler et al., 2018) (Figure 7).It should be noted that all studies but one (Regidor et al., 2022) included in the network considered the mean values of PPD and BOP around the treated implants (rather than worst site).

Indirect comparisons between arms that were not directly investigated by the studies are reported in Supplementary Material (Appendix 10).

- Secondary outcomes

Details on secondary outcomes can be found in Supplementary Material (Appendix 11, 12, 13, 14, 18).

Overall, none of the different reconstructive surgeries was associated with early side effects or adverse events beyond what would be expected for a minor surgical procedure. Amongst the most common complications reported by the included studies were the presence of early post-operatively soft tissue dehiscence and exposure of the barrier membrane. Roos-Jansaker et al. (Roos-Jansaker et al., 2007) reported that adding a synthetic resorbable membrane to a natural hydroxyapatite graft led to increased complications as compared to placing the graft only, including flap dehiscence (11% vs. 0%), wound instability at surgery (37.5% vs. 14.3%) and soft tissue craters at 2 weeks (82.4% vs. 78.9%). Moreover, membrane exposure occurred in 43.8% of the cases at 2 weeks and 34.3% of the cases at 7 weeks. A later study also suggested that the use of a native collagen barrier was associated with an increased risk for soft tissue dehiscence (19% vs. 0%), exposure of the barrier itself (9.5% vs. 0%) and of the

graft (4.8% vs 0%), as compared to the use of the graft alone (Regidor et al., 2022). The same study also reported that, at 2 weeks, the use of a graft alone was associated to significantly less pain (VAS median 20, interquartile range 70 vs. median 5, interquartile range 30) as compared to the combined use of a graft and collagen membrane (Regidor et al., 2022). It is not possible to speculate whether the risk of early complications and biomaterial exposure differed in case a submerged versus non-submerged protocol was followed, since only one study fulfilling FQ2 criteria clearly reported on a submerged healing protocol (Isler et al., 2022, Isler et al., 2018). Few studies (mainly studies with >12-month follow-up) indicated the number of implants that required additional procedures or had recurrence of peri-implantitis. In particular, Isler et al (Isler et al., 2022) reported that, at 3 years of follow-up, 9 implants (out of 25) treated with DBBM and concentrated growth factor membrane and 5 implants (out of 26) treated with DBBM and native collagen membrane had recurrence of peri-implantitis, while another study with a follow-up from 2 to 10 years reported that out of 170 implants, 18 required 1 additional surgery and 10 required two additional surgeries to reach the desired outcomes (Froum et al., 2015). Implant survival at 12 months ranged from 92% to 100%, but when considering composite outcomes for peri-implantitis resolution the range reported by the included studies was considerably wider (0% to 91% at 12 months, depending on how strict the parameters were) (see Supplementary Material, Appendix 13, 14). When adjusting for number of implants treated per subject, Aghazadeh et al. (Aghazadeh et al., 2012) indicated a higher likelihood (3.2) of success (defined as PPD≤5 mm, allowing one site with BOP, no suppuration at any implant surface and gain or no loss of alveolar bone) at 12 months when DBBM rather than autologous bone were combined with a collagen membrane to treat peri-implantitis defects. This trend was also confirmed at 5 years, where 36% of patients treated with autologous bone compared to 78.3% of patients treated with DBBM showed a successful outcome (Aghazadeh et al., 2022). Conversely, Regidor et al. reported similar disease resolution, defined as no BOP/SOP, PPD≤5mm and recession ≤1 mm when DBBM was associated or not with a native collagen membrane (Regidor et al., 2022).

4. Discussion

This systematic review evaluated the efficacy of reconstructive therapies for peri-implantitis defects. Based on a meta-analysis that included 4 RCTs (3 with some concerns and 1 with high risk of bias), reconstructive surgery and access flap surgery resulted in similar PPD reduction at 12 months post treatment, while reconstructive surgery resulted in improved radiographic bone level changes, thus corroborating the results of previous systematic reviews (Tomasi et al., 2019, Ramanauskaite et al., 2019). The wide prediction intervals calculated both for PPD changes and for radiographic changes suggested uncertainty on the overall effect of the two surgical approaches. In particular, caution is required in interpreting the radiographic results as the superior outcome in terms of bone level changes noted after reconstructive therapies does not necessarily indicate that trabecular bone filled the treated defects or that re-osseointegration occurred. Moreover, while between-study heterogeneity was moderate for PPD reduction, it was higher for radiographic changes. For the latter outcome, the asymmetric funnel plot (Supplementary Material, Appendix 6) suggests some evidence of publication bias, although the strength of this assumption is weak considering the low number of studies included in the meta-analysis. Similar improvements in terms of BOP and SOP were also noted. It is also important to highlight that our conclusions are based on 4 studies with some concerns for bias and 3 studies with high risk of bias (Figure 2), hence a certain level of caution needs to be applied when interpreting the findings. Moreover, two studies employed a material, titanium granules, which is not routinely used in clinical practice, hence the relevance of the findings of these studies is limited (Wohlfahrt et al., 2012, Andersen et al., 2017, Jepsen et al., 2016).

With respect to peri-implantitis resolution, different composite outcomes were assessed by the included RCTs, but, the majority of the studies did not indicate a benefit of reconstructive over access flap surgery and they suggested that only in a limited number of cases (14-35% of the cases, depending also on how stringent the parameters are) it is possible to achieve complete disease resolution. On the contrary, Renvert et al. (Renvert et al., 2018b) indicated enhanced peri-implantitis resolution (defect fill ≥1.0 mm, PPD values at implant ≤5 mm, no BOP, and no SOP) in cases where reconstructive rather than access flap surgery was performed (9/21 and 1/20 implants fulfilled the outcome, respectively). Nevertheless, and including the latter study, a very limited number of patients reached the desired outcome,

thus confirming how challenging and unpredictable peri-implantitis resolution is regardless of the surgical technique applied.

It is possible that the lack of significant clinical differences between reconstructive and access flap surgery suggested by the present review could be ascribed to the fact that we combined different reconstructive approaches, that ranged from titanium granules (Andersen et al., 2017, Wohlfahrt et al., 2012, Jepsen et al., 2016), to DBBM (or DBBM graft with 10% collagen) alone (Renvert et al., 2018b, Derks et al., 2022) or combined with a native collagen membrane (Renvert et al., 2021), to a beta-tricalcium phosphate graft formulated with prolonged release local doxycycline (Emanuel et al., 2020), or amelogenin (Isehed et al., 2018, Isehed et al., 2016). Additional sources of variability across studies included the definition of peri-implantitis applied, the use of different implant decontamination protocols and healing protocols (submerged vs. unsubmerged). Furthermore, the morphology of the defects, type of implant and implant surface were never adjusted for in the treatment allocation of the studies, which may have impacted on the healing outcomes. As such, while the meta-analysis aimed to provide an estimate of the comparison between reconstructive therapies and access flap, it should be interpreted with caution.

It should also be noted that our meta-analysis was limited to 12-month data, while the long-term stability of the outcomes achieved by AFS and reconstructive surgery is poorly investigated in RCTs. In a case series, a survival rate of 83.3% for SLA implants and 71.4% for plasma-sprayed implant was reported after 7 years of treatment with DBBM with 10% collagen (Roccuzzo et al., 2017), which reduced to 80% and 55% respectively at 10 years (Roccuzzo et al., 2020). Regardless of the surgical treatment applied, it is therefore expected that some patients will require additional treatments, some will lose implants or will develop complications over time.

No meta-analysis could be performed in relation to changes in recession level. However, the largest comparative study so far indicated that buccal recession was less pronounced after reconstructive surgery with DBBM with 10% collagen compared to AFS (0.7 mm vs. 1.1 mm) at 12 months, thus indicating that reconstructive surgery might be more appropriate in aesthetic areas (Derks et al., 2022). This outcome was not confirmed by three other studies with the same 12-month follow-up employing an alloplastic graft or DBBM alone or combined with a collagen membrane and including a significantly lower number of patients (Renvert et al., 2021, Renvert et al., 2018b, Emanuel et al., 2020). On the contrary, a recent systematic

review (Sanz-Martin et al., 2021) indicated less mucosal recession after reconstructive procedures (0.389 mm, 95% CI [0.204; 0.574]), compared to non-reconstructive surgeries (-1.35 mm; 95% Ci -2.62, -0.07) based on a meta-analysis performed on two arms from the same CCT (Deppe et al., 2007) and one RCT (Renvert et al., 2018b). It should be noted that the CCT included in the latter meta-analysis performed resection of soft tissue following implant decontamination (Deppe et al., 2007), hence it was not considered an access flap and not included in the current review.

When assessing overall the efficacy of reconstructive surgeries based on comparative studies (FQ2), we were not able to perform a Bayesian network meta-analysis owing to study heterogeneity in terms of biomaterials employed, as well as implant decontamination protocols, performance or not of implantoplasty and healing protocol. Nevertheless, based on the effect estimates for the direct comparisons of the included studies, we could not identify clear differences in terms of PPD and BOP changes between the different reconstructive therapies, nor could we establish a hierarchy between the different biomaterials. This is in line with the outcomes of the recent FDI consensus report (Khoury et al., 2019). Rather than the biomaterials employed, the history of periodontitis, morphology of the defect (vertical depth, number of intrabony defect walls) and adherence to supportive care may be factors playing a more significant role on treatment success (Schwarz et al., 2010, Isler et al., 2022). It is however important to note that the outcomes of our network meta-analysis resulted from the combination of only 4 RCTs, which had intrinsic limitations and did not consider the whole plethora of biomaterials and bioactive factors that have been documented in the literature.

Besides clinical/radiographic outcomes, other relevant endpoints to consider are the risk of complications and PROMs. In this respect, a CCT indicated that adding a synthetic resorbable membrane to a natural hydroxyapatite graft led to a remarkable increased rate of complications as compared to placing the graft only, including flap dehiscence (11% vs. 0%), wound instability at surgery (37.5% vs. 14.3%) and soft tissue craters at 2 weeks (82.4% vs. 78.9%) and membrane exposure occurred in 43.8% of the cases at 2 weeks and in 34.3% of the cases at 7 weeks (Roos-Jansaker et al., 2007). It is possible that this high incidence of complication might relate to the surgical technique adopted, experience of the operator, post-operative care and patient selection. Nevertheless, Regidor et al. (Regidor et al., 2022)

also suggested that adding a collagen membrane to a DBBM graft with 10% collagen increased surgical time (approximately 10 minutes), as well post-surgical complications (soft tissue dehiscence, exposure of the barrier and/or graft) and patient-reported pain 2 weeks after surgery. These outcomes are in line with a previous study by Khoury and Buchmann (Khoury and Buchmann, 2001) that reported a higher risk of complications when membranes are applied in association with a bone graft, particularly if they are non-resorbable (60% presented early dehiscence, exposure, fistula or sequester formation). Likewise, Roos-Jansaker (Roos-Jansaker et al., 2007) indicated a 43.8% rate of membrane exposure at 2 weeks after surgery and a higher percentage of wound instability at surgery when an algae-derive hydroxyapatite was covered by a resorbable membrane. No benefit in terms of 5-year clinical and radiographic parameters was also documented by the same authors when adding a barrier (Roos-Jansåker et al., 2014).

Whether a submerged healing should be preferred after reconstructive surgery remains an open question. The main advantage of submerged healing would be to achieve primary wound closure and to promote an aseptic healing environment, which are crucial factors for stabilizing the blood clot, improving graft stability, and maximizing the regenerative potential of the intrabony compartment, as per GBR principles (Wang and Boyapati, 2006, Retzepi and Donos, 2010). On the other hand, unsubmerged healing eliminates the need of prosthesis removal, reducing treatment time, costs and possibly the overall complexity of treatment. Removal of the prosthetic supra-structure before peri-implantitis surgery has been performed in some of the included studies (Table 2, 3). This approach clearly facilitates surgical access to the implant surface, and hence likely enables effective decontamination.

Irrespective of the healing modality, the importance of creating a firm peri-implant soft tissue seal has been emphasized. Although the existing evidence is conflicting regarding the influence of keratinized mucosa on the surgical outcomes of peri-implantitis (Ravida et al., 2020), clinicians should carefully assess the pre-operative soft tissue and, in cases of peri-implantitis, they may consider the need to perform soft tissue reconstructive procedures whenever the quality or quantity of soft tissue is not adequate (Monje et al., 2020, Roccuzzo et al., 2011).

This systematic review is not free of shortcomings. Considering that there is evidence from the literature that uncontrolled diabetes can impair bone formation (Retzepi et al., 2018,

Retzepi and Donos, 2010, Camargo et al., 2017), and osseointegration (Javed and Romanos, 2009, Saito et al., 2022) and that uncontrolled diabetic patients can have an increased risk of developing peri-implantitis (Monje et al., 2017), we decided to exclude studies including such patients. It should however be noted that other included studies included patients with hypertension, cardiovascular diseases, or other medical conditions. We do not know how these underlying conditions might have impacted on the study outcomes.

In addition to the heterogeneity amongst the included studies in terms of biomaterials and surgical protocols already discussed, it should be highlighted that the performance of NST before surgical treatment was inconsistently reported, ranging for instance from no details provided, to simple irrigation of the implant with a solution of piperacillin/tazobactam (Gonzalez Regueiro et al., 2021) or cleaning of implant shoulder (Roccuzzo et al., 2021, Roccuzzo et al., 2016), to the use of titanium curettes together with polishing (Derks et al., 2022) or air-polishing (Regidor et al., 2022) (Table 1). Remarkably, a recently published study did not demonstrate an added effect of performing sub-marginal instrumentation compared to supra-gingival instrumentation 6 weeks before surgical treatment of peri-implantitis-related defects in terms of 12-month PPD change and treatment success (Romandini et al., 2022).

The configuration of peri-implant defects, as well as implant surface characteristics differed between studies, with a potential influence on healing outcomes. Several studies have suggested that defect morphology can influence the healing potential following reconstructive therapy, with defect fill more likely at circumferential and 4-wall defects (Aghazadeh et al., 2012, Schwarz et al., 2010). While the limited clinical studies do not allow to make assumptions regarding the possible impact of implant material on peri-implantitis progression (Schwarz et al., 2021, Stavropoulos et al., 2021), two recent reviews based on pre-clinical studies indicated that peri-implantitis occurs independently from implant surface, but implant surface characteristics play a critical role on the progression and treatment outcomes. In particular, turned surfaces are associated with less bone loss during the progression period and greater bone gain after treatment (Stavropoulos et al., 2021, Garaicoa-Pazmino et al., 2021). None of the comparative studies included in this review controlled for implant surface distribution in the treatment allocation.

An additional source of bias amongst the included studies (for both FQs) was the quality and adherence to supportive care programs. While few studies clearly indicated that patients

were part of strict and regular recall programmes, which included regular mechanical debridement, motivation and instructions, other studies failed to provide details or discharged the patients back to their general dentists (Table 1). As a matter of fact, based on the 6th ITI Consensus, peri-implantitis treatment protocols that include individualized supportive care result in high survival of implants after 5 years, with about three-quarters of implants still present (Heitz-Mayfield et al., 2018). As recently suggested by Roccuzzo et al. (Roccuzzo et al., 2021), adherence to supportive periodontal implant care (SPIC) can increase the 5-year treatment success even in case of defects with a less favourable morphology. It was not possible to compare SPIC protocols applied by the different studies, also considering that in a number of cases SPIC included additional non-surgical or surgical treatments to address the presence of clinical signs of inflammation. For instance, Froum et al. (Froum et al., 2015) indicated that in a consecutive series of 170 implants in 100 patients with 2- to 10-year follow- up, 18 implants required one additional surgery, and 10 implants required two additional surgeries to reach the desired outcomes.

Finally, an additional source of bias relates to the inconsistent use of systemic antibiotics and post-operative regime followed (Table 2 and 3). In case of reconstructive therapies, the rationale for adjunctive systemic antibiotics can relate to the prevention of biomaterial infection, but to the best of our knowledge no RCTs have investigated their contribution and which regime is more effective.

Clinicians must consider that an indiscriminate empiric antibiotic regimen promotes the development of antimicrobial resistance, which may also escalate peri-implant disease (Verdugo et al., 2016). Moreover, unwanted side effects are often associated with systemic antibiotic administration, particularly in case of prolonged administration. As such, it is recommended that future studies should clarify if systemic antibiotics have an impact on peri-implantitis treatment, in which situations they provide a tangible clinical benefit and which regime is more effective.

In conclusion, and within the limitations of the current review, it is suggested that:

- Both access flap surgery and reconstructive surgery can significantly improve peri-implant clinical parameters at 12 months follow-up, with reconstructive surgeries leading to improved radiographic outcomes (despite the limitations described above in relation to this outcome). A careful assessment of peri-implant defect anatomy

should be performed before opting for a reconstructive surgery. While it was beyond the remit of this review to provide indications related to the impact of the intrabony component of the defect in terms of number of walls and defect morphology on the treatment outcome, these characteristics may play a crucial role when deciding on the surgical approach to be applied.

- Irrespective of the surgical approach and biomaterial employed, resolution of peri-implantitis is challenging to achieve; in the long term, it is expected that a number of implants will develop disease recurrence, which may require additional surgical procedures or could lead to implant loss.
- Potential aesthetic and patient-reported advantages of reconstructive therapies have been poorly investigated and should be explored by future studies.
- While there is currently not enough evidence to establish a hierarchy of efficacy between different types of reconstructive therapies, few studies suggest that the use of a barrier might increase the rate of early complications, including soft tissue dehiscence and exposure of the membrane/graft. Future RCTs are needed to clarify the clinical indications for membrane/barrier use, and to establish which grafts are more effective.
- Future studies should apply composite outcomes to assess peri-implantitis resolution, which should include clinical measures of inflammation and radiographic assessments of bone-level alterations (Sanz et al., 2012).

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Authors contribution

ND contributed to the development of the review protocol, he was the third reviewer in case of disagreement in the selection process and contributed to drafting the article and interpreting the data

EC contributed to the development of the review protocol, paper screening, data extraction, risk of bias, drafting of the article and data interpretation

MG contributed to paper screening and data extraction

MB contributed to the development of the review protocol, statistical analysis, drafting of the article and data interpretation

VS contributed to development of the review protocol, paper screening and data interpretation

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Figure legend

Figure 1 Flowchart of the study selection process (adapted from (Page et al., 2021)).

Figure 2: Details of risk of bias assessment performed for RCTs answering FQ1 with RoB2.

Figure 3 Details of risk of bias assessment performed for RCTs answering FQ2 with RoB2.

Figure 4: Details of risk of bias assessment performed for prospective case series included in FQ2 with ROBINS-I.

Figure 5: Forest plot of the studies included in the meta-analysis on the difference between mean PPD changes under access flap surgery and reconstructive surgery (FQ1); the diamond indicates the overall random effects meta-analytic estimate. Since the primary endpoint considered was the difference between the mean change for access flap surgery compared to reconstructive surgery, negative values favor reconstructive surgeries (left side of the "no effect" line).

Figure 6: Forest plot of studies included in the meta-analysis on the difference between mean changes in radiographic bone levels under access flap surgery and reconstructive surgery (FQ1); the diamond indicates the overall random effects meta-analytic estimate. Since the primary endpoint considered was the difference between the mean change for access flap surgery compared to reconstructive surgery, negative values favor reconstructive surgeries (left side of the "no effect" line).

Figure 7: Network for PPD and BOP changes based on 4 studies. A, DBBM/DBBM with 10% collagen; B, DBBM/DBBM with 10% collagen + collagen membrane; C, bovine-derived hydroxyapatite ceramic with small granule size; D, DBBM+ concentrated growth factor membrane; E, autologous bone + collagen membrane. Mean difference in PPD and BOP change are reported only for the direct comparisons (continuous lines). The mean difference in BOP change between B and E was not reported due to a discrepancy in the results in the original paper (Aghazadeh et al., 2012).

Table legend

Table 1: Table 1: Demographics and main characteristics of the included studies. Recon, reconstructive surgery; AFS, access flap surgery; NST, non-surgical therapy; SPC, supportive periodontal care; SOP, suppuration; BOP, bleeding on probing; PPD, probing pocket depth; OHI, oral hygiene instructions; GDP, general dental practitioner

Table 2: Characteristics of the interventions performed in the studies included for FQ1. DBBM, deproteinized bovine bone mineral; Recon, reconstructive surgery; AFS, access flap surgery

Table 3: Characteristics of the interventions performed in the studies included for FQ2. PDGF, platelet-derived growth factor; Recon, reconstructive surgery; DBBM, deproteinized bovine bone mineral; EMD, enamel matrix derivative; KT, keratinized tissue; sCTG, subepithelial connective tissue graft; EDTA, ethylenediaminetetraacetic acid; PDT, photodynamic therapy.

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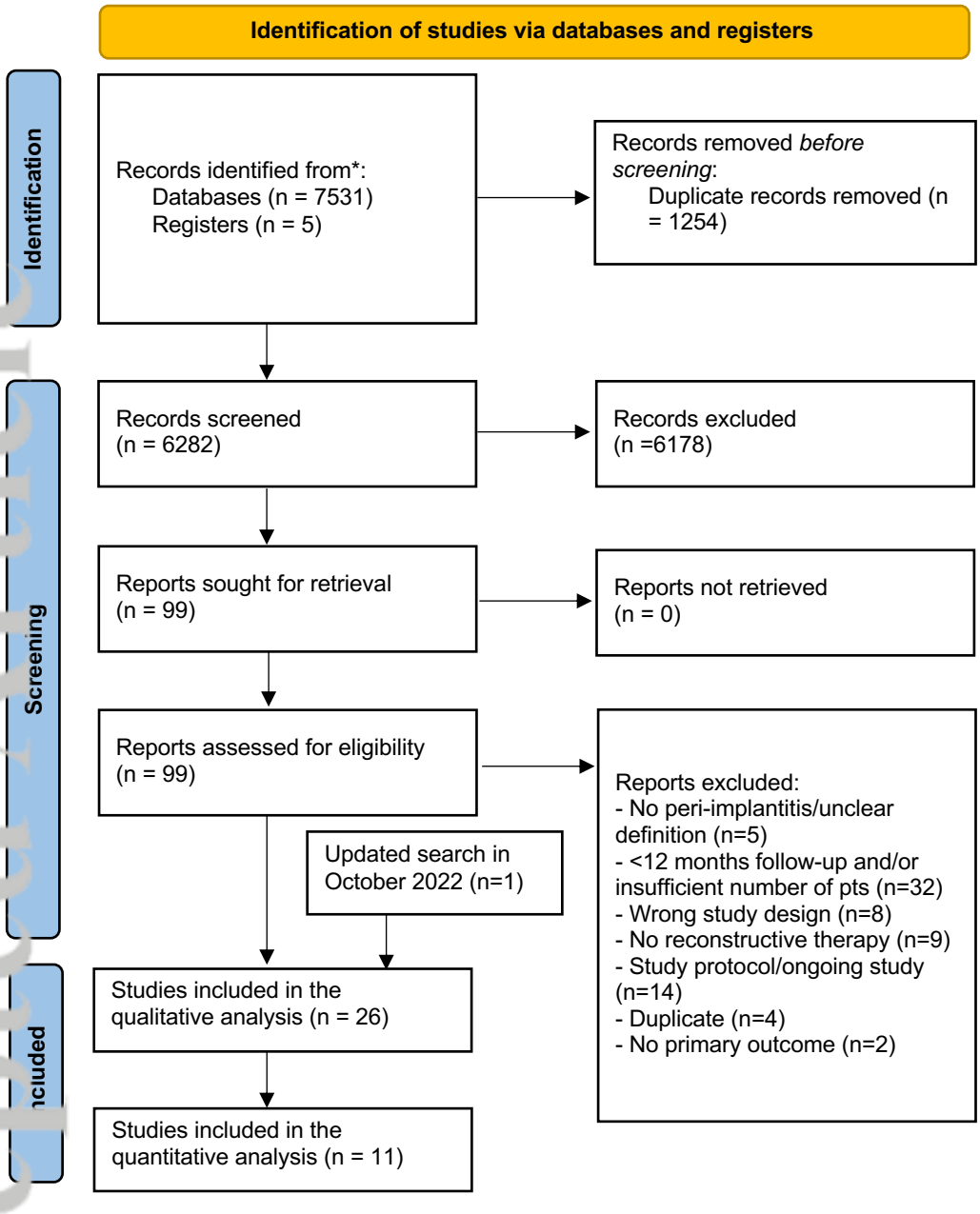

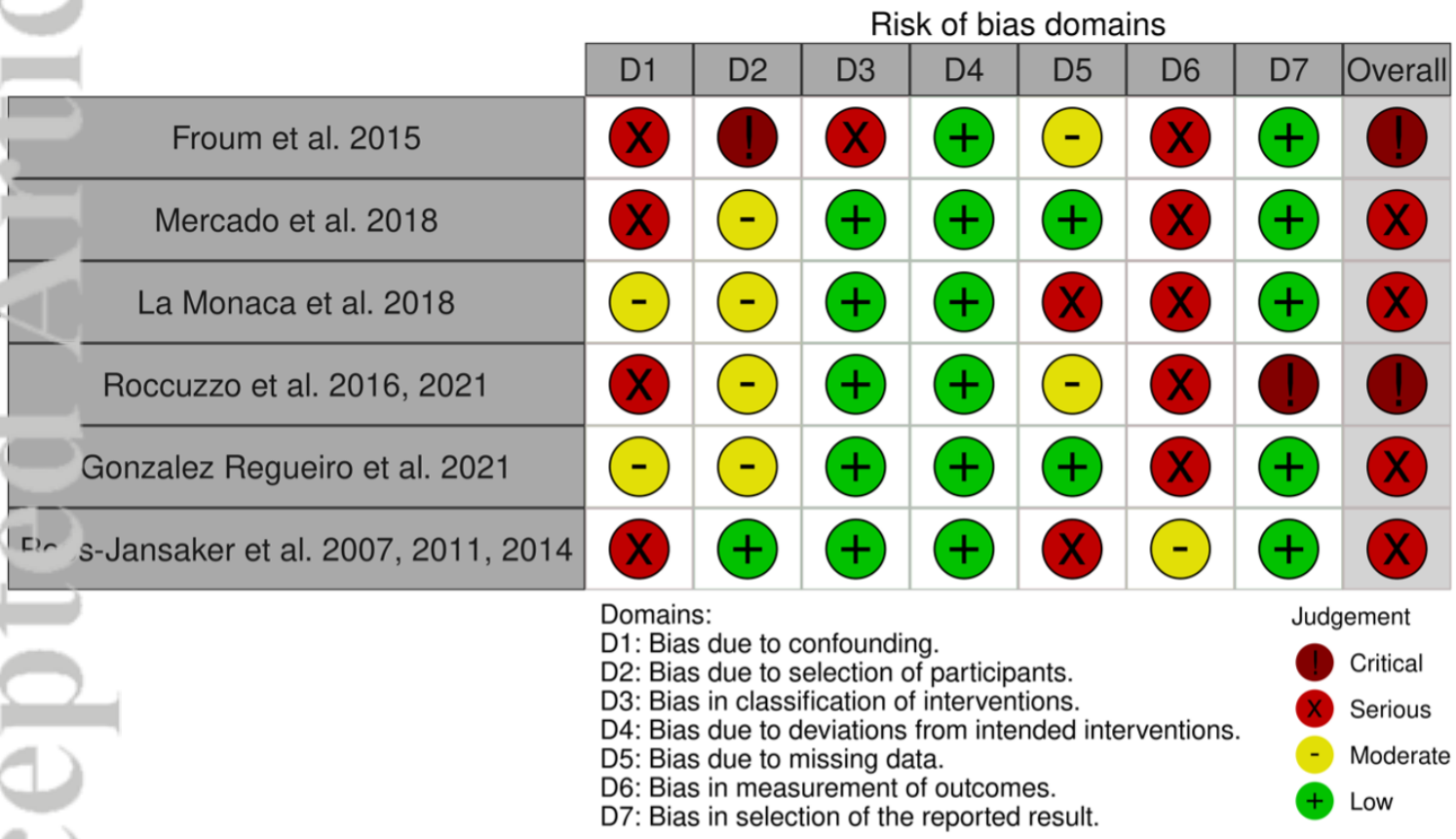

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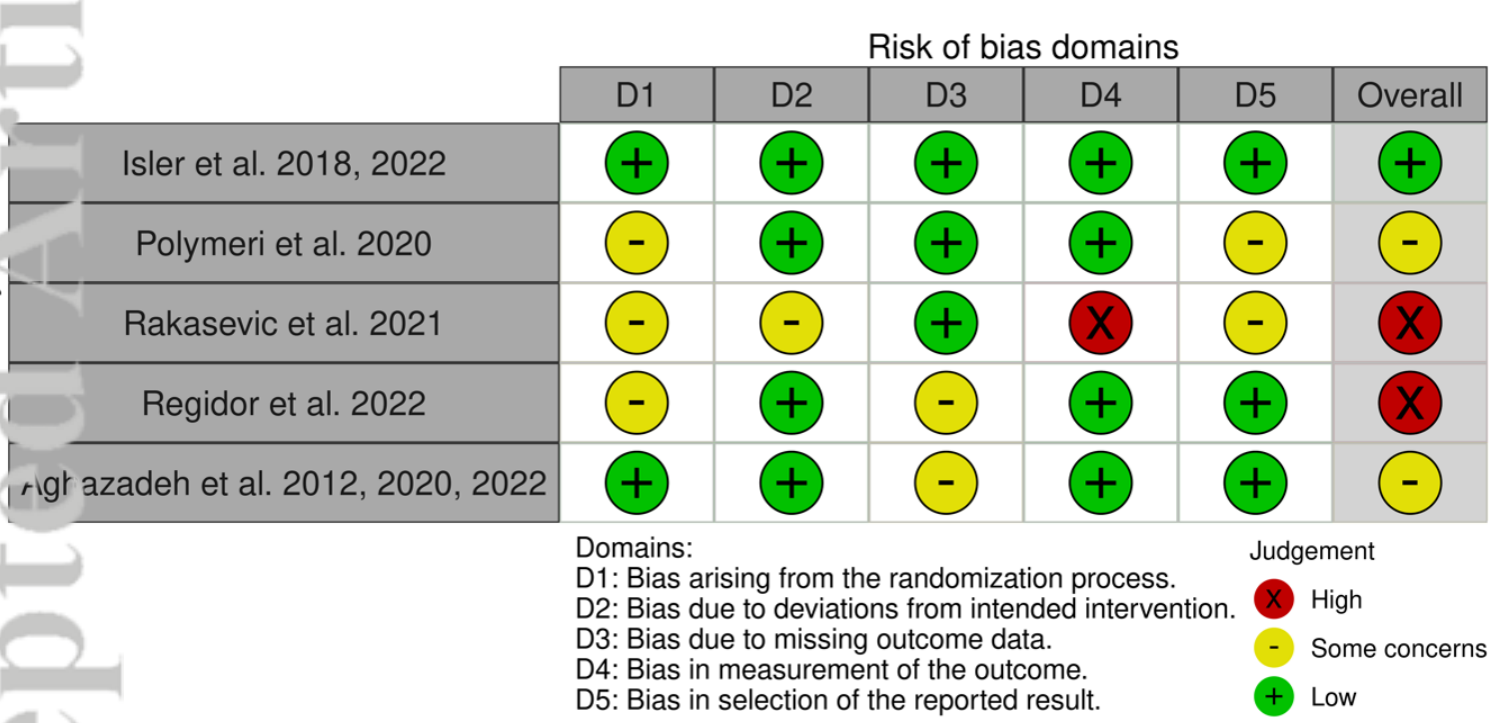

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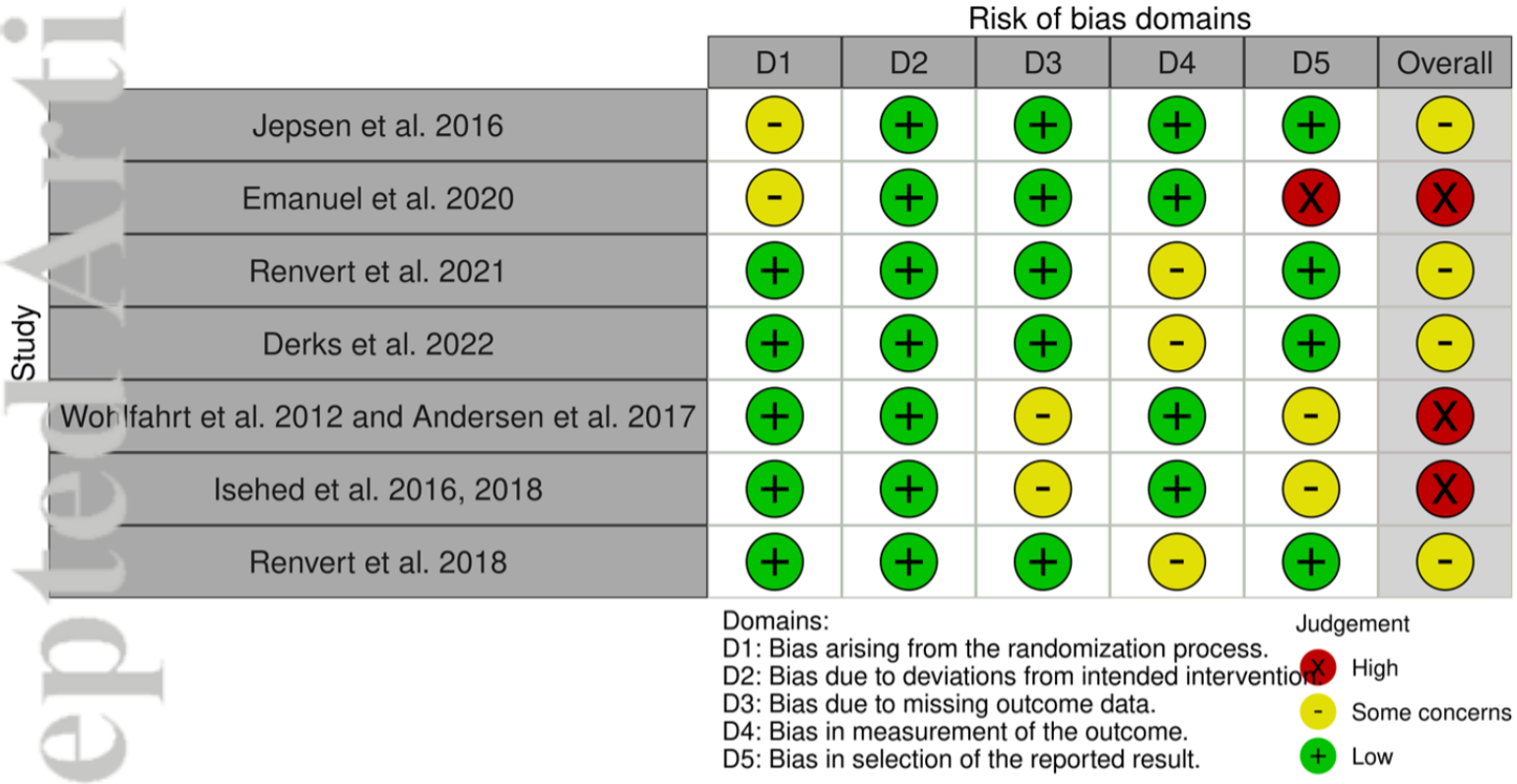

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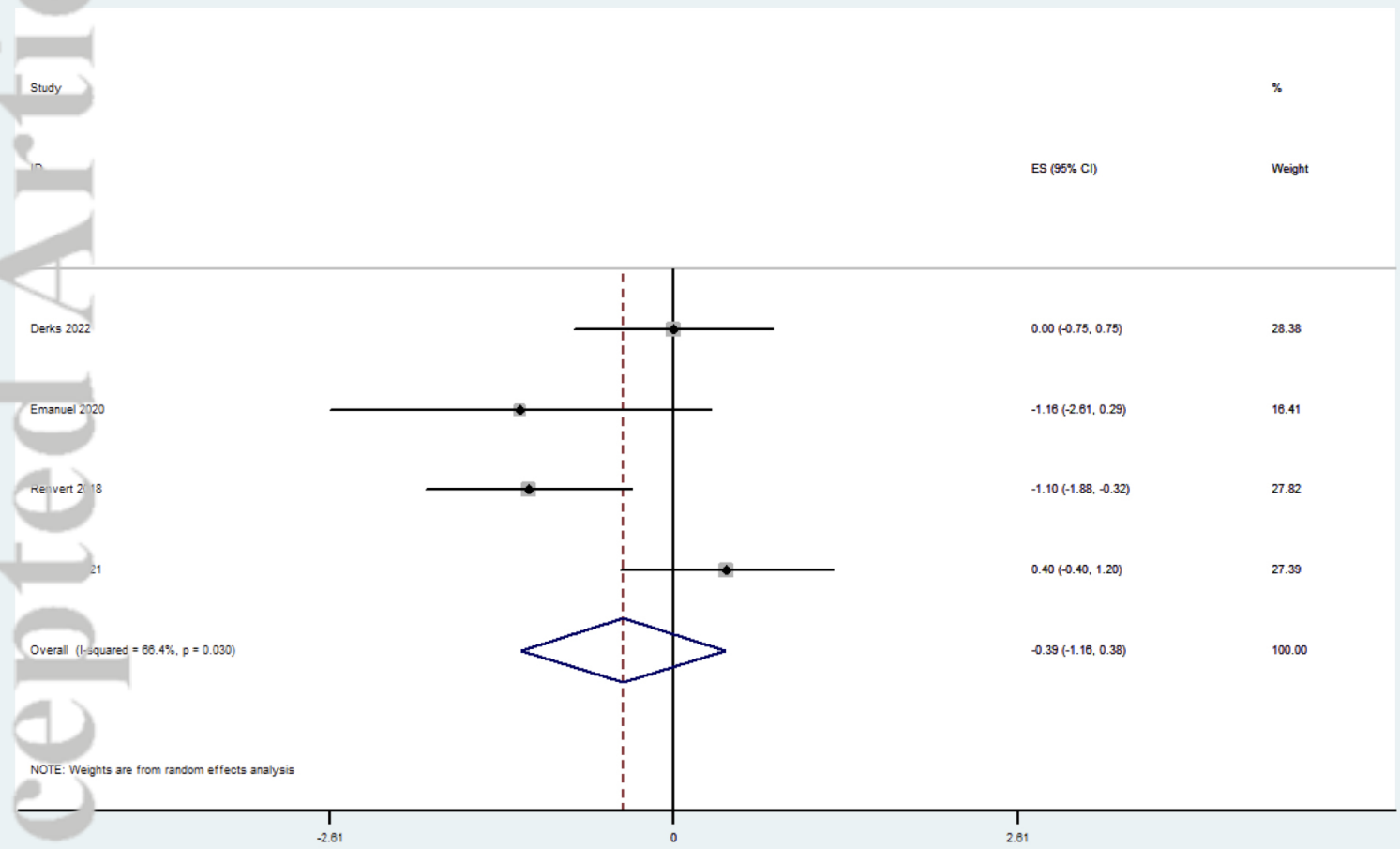

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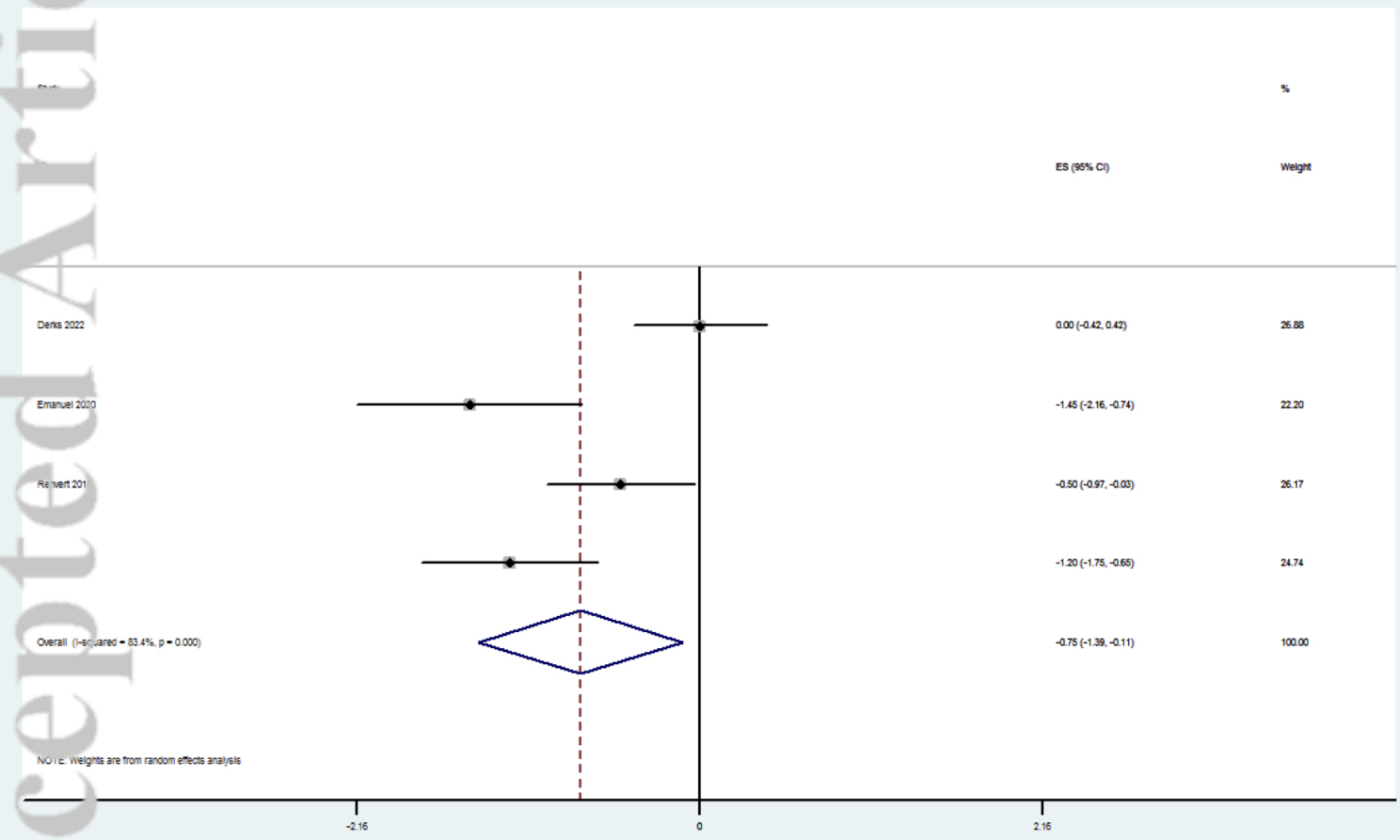
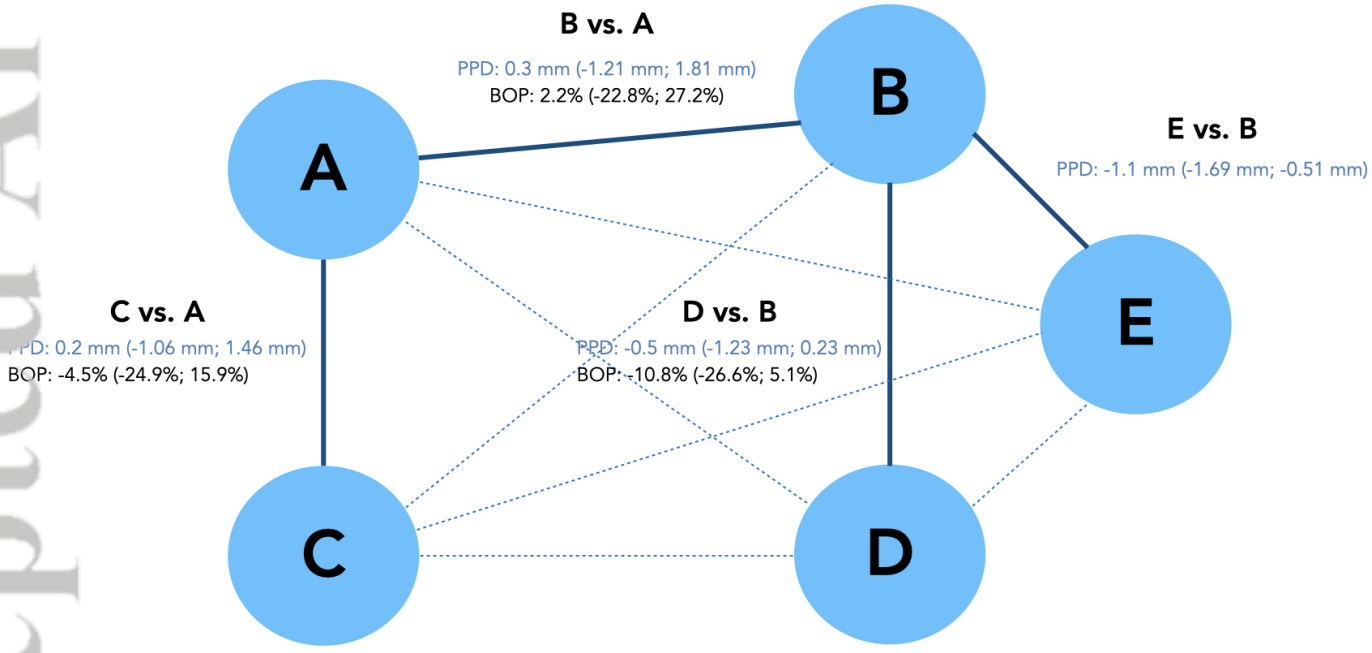


Test of ES=0 : z= 2.29 p = 0.022; I-squared (variation in ES attributable to heterogeneity) = 83.4%

JCPE_13775_Figure 6.jpeg



JCPE_13775_Figure 7.jpeg

Study	Study design; Country	Setting; source of funding	Peri-implantitis definition	N. pts with outcomes/ dropouts	Age; M/F	Smoking status (S/NS/F) / Systemic diseases	History of periodontitis	Was NST performed before surgery? (Y/N/NI; protocol	Details about SPC	Study follow-up	Implant system/ implant surface	Type of prosthesis	Time implants in function
Focused question 1													
(Wohlfahrt et al., 2012, Andersen et al., 2017)	RCT; Norway	University; grant from industry (Tigran AB) and partly from Norwegian Research Council	PPD≥5 mm with BOP and an infrabony component of the peri-implant osseous defect as judged on radiographs	32/1 at 12 months; 12/21 at 7 years	Recon: 65.0± 10.0; 7/9; AFS: 57.2 ± 12.3; 7/10	Recon: 6/2/8, AFS: 10/5/2 / 1 patient had type 1 diabetes and 3 patients had type 2 diabetes but Hb1AC <6.5	Recon: 11 (68.8%), AFS: 6 (35.3%)	NI but periodontal treatment was completed before the study (no mention of NST on the implants)	OHI and supragingival debridement given at 3, 6 and 9 months in the university, then 11/12 pts received SPC with their GDP/hygienist every 6-12 months	12 months, 7 years	Recon: Astra (4), Nobel Mark III (9), Nobel Replace (1), Straumann (2); AFS: Astra (5) Nobel Mark III (5), Nobel Replace (2), Straumann (4), Frialit (1)/ Recon: Micro-rough (7) – hydrophobic (5), unclear (2). Unclear type of surface (9) AFS: Micro-rough (12) – hydrophobic (8), unclear (4). Unclear type of surface (5)	24 screw-retained, 7 cement-retained, 2 OVD retained by implants	≥12 months
(Jepsen et al., 2016)	Multi-center RCT; Germany, The Netherlands, Italy, Spain, Sweden	University; research grant from Industry (Tigran Technologies AB)	intraosseous defect ≥3mm and one of the following: PPD≥5mm, BOP and/or SOP	59/4	58.4 ± 12.3 (Recon: 57.7±12.6, AFS: 59.1±12.2; 27/36; (Recon: 16/17; AFS: 11/19)	18/25/20 (Recon: 11/13/9; AFS: 7/12/11) / diabetes mellitus (hemoglobin A1c ≥6.5), use of corticosteroids or other anti-inflammatory prescription drugs, use of medications known to induce gingival hyperplasia were exclusion criteria	37 (Recon: 17, AFS: 20)	Y, OH instructions and NST of teeth and implants	supragingival debridement and OHI provided as needed at 6 weeks and 3, 6, 9, and 12 months after surgery	12 months	Recon: Ankylos (2), Astra OsseoSpeed (6), Dyna (1), Friadent Xive (1), Nobel Biocare (10), Straumann standard neck (5); TMI (3), Zimmer (4), Biomet 3i (1) AFS: Ankylos (1), Astra OsseoSpeed (4), Friadent Xive (2), Nobel Biocare (8), SIC Invent (1), Straumann standard neck (5), Tri-MAX (1), TMI (2), Zimmer (2), Biomet 3i (4)/	NI	>12 months

											Recon: Micro-rough (23) – hydrophobic (18), unclear (5). Unclear type of surface (10) AFS: Micro-rough (22) – hydrophobic (17), unclear (5). Unclear type of surface (8)		
(Renvert et al., 2018b)	RCT; Swede n	Private practice (Specialty Clinic for Periodontolog y at Region Skåne); Industry (Zimmer Biomet) and Research Foundation at Kristianstad University	PPD ≥5 mm combined with BOP/suppurat ion and peri-implant marginal bone loss	41/1	Recon: 67.5±11. 3; 8/13; AFS: 70±7.8; 5/20	Recon: 5S/21NS, AFS: 5S/20NS/ diabetes mellitus (blood sugar level ≥53.0 mmol/L), an anti-inflammatory prescription including prednisone and any known medication with known side effects on gingival growth were exclusion criteria. 5% of Recon and 15% of AFS had diabetes, 36% of Recon and 40% of AFS had elevated blood pressure and 55% of Recon and 45% of AFS had a medical diagnosis. Only 36% of Recon and 55% of AFS were not taking any medication	Unclear, but any periodontal infection in the remaining dentition was treated before enrolment.	NI, but any periodontal infection in the remaining dentition was treated before enrolment (no mention of NST on implants)	Based on individual needs, professional prophylaxis was performed every 3rd month	12 months	Branemark (8 Recon, 11 AFS); AstraTech (9 Recon, 7 AFS), unknown (3 Recon, 2 AFS), Cresco (1 Recon, 0 AFS) / Recon: micro-rough 18, unknown 3; AFS: micro-rough 18, unknown 2	NI	NI
(Isehed et al., 2018, Isehed et al., 2016)	RCT; Swede n	Hospital; self-funded by the authors and their institution	PPD≥5 mm and BOP and/or SOP and at least one implant with angular peri-implant bone loss	25/4 at 12 months; 18/11 at 3 years; 14/15 at 5 years	Recon: median 70 (min-max 61-81); 6/9; AFS: median 73.5 (min-max	10S/19NS (Recon 4S/11NS; AFS: 6S/8NS) / uncontrolled diabetes (HbA1c > 63 mmol/ mol), intake of antibiotics or anti-inflammatory	15 patients lost teeth due to periodontitis; % of dental bone support (% of root length):	NI, but periodontal disease was treated with mechanical debridement and OHI (no mention of	Maintenance at 6 weeks and every third month until 12 months after surgery, then every 3- or 6- month interval according to individual needs at	12 months, 3 and 5 years	Recon: 1 Nobel turned, 8 Astra, 5 Straumann SLA, 1 3i; AFS: 1 Nobel turned, 5 Nobel TiUnite, 5 Astra, 3 Straumann SLA/	Probably all screw retained	Recon: median 8 years (min-max 3-16 years); AFS: median 6.5 years (min-max 2-13)

			≥3 mm measured on X-ray		67-83); 5/9	medication during the past 3 months, or using drugs causing gingival hyperplasia were exclusion criteria. 19 patients were taking unspecified medications and 1 had controlled diabetes[Ψ]	median 72% (min-max 62-82%) for Recon and median 65.5% (min-max 58-80%) for AFS	NST on implants)	specialist clinic or by GDP		Recon: polished (1), micro-rough hydrophobic (14); AFS: polished (1), micro-rough hydrophobic (13)		
(Emanuel et al., 2020)	Multi-center RCT; Israel	Hospital/ University; industry (PolyPid Ltd - one of the authors is shareholder and another is scientific director)	PPD of 6 to 10 mm, BOP with or without SOP and radiographic evidence of bone loss >2mm	27/0	64.81±7.61; 11/16	0S/27NS (non-smokers = less than 5 cigarettes a day) / uncontrolled diabetes excluded	NI but severe active periodontitis excluded	NI	NI	12 months	All micro-rough but not TPS, not HA-coated / no further information provided.	NI	NI
(Renvert et al., 2021)	Multi-center RCT; Sweden, France, Germany	University/Hospital and private practice; Research Foundation of Kristianstad University and Industry (Geistlich Pharma AG)	PPD≥5 mm with BOP/SOP; a radiographic intra-osseous defect≥3 mm	66/5	Recon: 62.2±10.2; 17/20; AFS: 62.9± 13.0; 17/17	Recon: 8S/29NS; AFS: 9S/25NS / HbA1c >7; taking prednisone or other anti-inflammatory prescription drugs were exclusion criteria	Unclear, but periodontal disease was treated and no pockets >5mm were present	Y, instruction in OH measures and debridement of teeth and implants	OHI at 3,6,9 ,12 months	12 months	NI / Micro-rough (modified) (36 Recon and 32 AFS); Polished (non-modified) (1 Recon and 2 AFS)	Unclear number but both screw-retained and cemented	≥12 months
(Derks et [illegible]2022)[£]	Multi-center RCT; Sweden, Italy, Spain, Germany	University/Hospital and private practice; Large Clinical Grant from the Osteology Foundation	PPD≥7 mm, BOP/SOP and radiographically confirmed bone loss of ≥3 mm.	128/5	60.6±11.6; 49/84 (Recon: 62.1±11.4; 28/39; AFS: 59±11.7; 21/45	35/98 (Recon: 16/51; AFS: 19/47) / systemically healthy (diabetic patients excluded from the analysis upon request to the authors)	87; Recon 1: 44; AFS 2: 43	Y, OHI and instrumentation performed with titanium curettes and polishing cups	OH reinforcement and polishing by rubber cup at 6 weeks, 6- and 12-months post-surgery	12 months	Nobel Biocare (25); Astra Tech (59); Straumann (31); Other (18); Unclear (9) / Micro-rough (90) – hydrophobic (31), unclear (59). Unclear type of surface (52)	Cemented: 62; conometric: 4; screw-retained: 76	10.3±5.5 years
Focused question 2													
(Roos-Jansåker et al., 2014,	CCT; Sweden	Mixed Speciality Clinic of	progressive loss of ≥3 threads	36/2 at 1 year; 32/6 at 3	Recon 1: 65.6±7.4 9/10	Recon 1: 12/1/4; Recon 2: 12/2/4 / Three patients	18 patients lost teeth due to	NI, but periodontal treatment	Full-mouth plaque scores were obtained and shown to the	1, 3 and 5 years	Branemark and Astra/	NI	NI

Roos-Jansaker et al., 2011, Roos-Jansaker et al., 2007)		Periodontology, Public Dental health Services and Kristianstad University; research foundations from the Public Dental Health Service, County of Skane, Sweden and Kristianstad University	(1.8 mm) following the first year of healing, in combination with bleeding and/or pus on probing, were involved in the study	years; 25/13 at 5 years	Recon 2: 66.3±6.8; 7/12	reported diabetes at baseline and one at 1 year and authors confirmed they all had controlled diabetes (HbA1c<7)*. 6 patients had coronary heart disease	periodontitis, 2 lost teeth for other reasons and 16 do not know. Periodontitis defined as bone loss of ≥4mm at existing teeth or at teeth before extraction was evident in around 69% of the teeth in both groups.	provided to teeth (no mention of NST on implants)	patient and re-motivation and re-instruction in OH procedures were performed if necessary every 3 months by a hygienist. Teeth and implants were cleaned using a rubber cup and low-abrasive paste.		Recon 1: Machined (27), rough (1); Recon 2: machined (35), rough (1)		
(Froum et al., 2015)	Prospective case series$^{\Psi}$; USA	Private practice; NI	BOP, PPD≥5mm and peri-implant bone loss ≥3mm	100/0	58.08 (20-83); 47/53	19 S/151 NS (NS defined as smoking <10 cigarettes a day) / patients with systemic diseases or taking medications that would cause a poor bone healing response (i.e. intravenous bisphosphonates, chemotherapy, recent radiation therapy) were excluded	NI, but patients received all necessary periodontal treatment prior of the surgery	NI, but all necessary periodontal treatment completed 1 month before surgery (unclear if this includes implants)	Maintenance every 8 to 12 weeks	2 to 10 years (mean 3.60±1.86)	For the 38 patients belonging to (Froum et al., 2012): Biomet 3i (21), Nobel Biocare (12), IMZ (4), Zimmer (3), BioHorizons (2), Frialit (2), Straumann (2), AstraTech (20), Bicon (2), Innova (1) / Micro-rough (57) – hydrophobic (55), unclear (2). Unclear type of surface (12)	NI	≥3 years
(Roccuzzo et al., 2016, Roccuzzo et al., 2021)	Prospective case series; Italy	Private practice; no funding	Peri-implantitis crater-like lesion with PPD ≥6 mm and no implant mobility	71/4 at 12 months; 51/11 at 5 years	57.8±8.5; 39/36	11S/64NS / systemically healthy	All patients previously treated for periodontitis	Y, cleaning of implants shoulders	Individually tailored SPC programme where motivation, reinstruction, supragingival instrumentation and antiseptic therapy and reduction in modifiable risk	12 months. 5 years	SLA Straumann tissue level implants / Micro-rough - hydrophobic	NI	NI

									factors were performed as needed				
(Isler et al., 2018, Isler et al., 2022)	RCT; Turkey	University/ Hospital; NI	Presence of a peri-implant marginal bone loss ≥2 mm based on baseline periapical radiographs after delivery of the final restoration and BOP and/or SOP with or without concomitant deepening of peri-implant pockets	52/5 at 12 months; 51/6 at 3 years	Recon 1: 57.96±9.07; 16/10; Recon 2: 56.15±9.23; 11/15	Recon 1: 6/20; Recon 2: 9/17 / serious systemic diseases, medications or conditions that would contraindicate for periodontal surgery and compromise wound healing were exclusion criteria	Recon 1: 11 (42.3%); Recon 2: 13 (50%)	Y, supra and subgingival /mucosal mechanical debridement	Supragingival/mucosal mechanical debridement and reinforcement OHI every 3 months during the first year. When necessary, localized subgingival/mucosal instrumentation in combination with pocket irrigation using saline solution was done except for the area of surgery. Later, individual SPC and nonsurgical approaches were applied at signs of recurrence in the whole mouth every 3–6 months according to the patient's risk profiling.	12 months, 3 years	Zimmer Tapered Screw-Vent, Straumann, Astra Tech, Xive S plus, Nobel Biocare Replace Select, Adin, MIS. / All microrough – hydrophilicity unclear as number of SLActive surfaces not specified	NI	Recon 1: 4.82±1.81 years; Recon 2: 5.21±2.48 years
(La Monaca et al., 2018)	Prospective case series; Italy	University/ Hospital; NI	Progressive bone loss of ≥3 mm detected on standard intraoral radiographs and presence of BOP or SOP	34/10	54.06±10.81; 15/19	25NS/9F / uncontrolled medical conditions, systemic diseases that could influence the outcome of the therapy (i.e., diabetes with HbA1c ≥6.5%, osteoporosis, or bisphosphonate medication), pregnant or nursing were exclusion criteria	13 had history of periodontal treatment, 3 unknown, 18 no history of periodontal treatment	NI, but supra and submucosal mechanical debridement and polishing, as well as motivational reinforcement performed (unclear if this includes implants)	OHI and supragingival debridement, motivational encouragement and instructions to maintain high levels of OH at 1, 3, 6, 9, and 12 months, then every 6 months.	1, 2, 3, 4, 5 years	All Nobel BioCare TiUnite / Micro-rough - hydrophobic	NI	50.62±22.96 months
(Mercado et al., 2018)	Prospective case series*;	University/ Hospital; National Health and	crater- like or circumferential defect, a	30/0	44.9±11; 36%/64%	0S/30NS / uncontrolled diabetes and bisphosphonate	Unclear, but periodontal treatment	NI, full-mouth ultrasonic debridemen	full-mouth ultrasonic debridement and prophylactic clean	1, 2 and 3 years	Branemark TiUnite 46.66%, Astra Tech 26.66%, Straumann	NI	9±3.8 years

	Australia	Medical Research Council Australia	BOP/SOP pocket >4 mm, ≥20% alveolar bone loss and in function for at least 2 years			medications were excluded	provided prior to the surgery as needed	t and manual curettage as needed (with or without local anaesthesia) 4–6 weeks before the surgical protocol (unclear if this includes implants)	and polish with rubber cap and pumice at 3, 6, and 12 months, and then every 4 months. Additional manual curettage (with or without local anaesthesia) using Gracey curettes and ultrasonic instruments was performed on the affected implant or dentition if there was BOP/SOP.		10%, Other 16.66% / Micro-rough – hydrophobic (73%), unclear (10%). Unclear type of surface (16.66%)		
(Aghazadeh et al., 2020, Aghazadeh et al., 2012, Aghazadeh et al., 2022)	RCT, Sweden	Private practice; Industry (Biomet 3i)	radiographic loss of bone ≥2 mm following placement of implant supra-structure, PPD≥5mm and BOP/SOP	45/0	Recon 1: 70.1±6.2; 36.4%/63.6% Recon 2: 67±7.5; 43.5%/56.5%	Recon 1: 40.9% smoker; Recon 2: 69.6% smokers	66.7% Recon 1 and 95.2% Recon 2 lost teeth due to periodontitis. Any periodontal disease around teeth was treated so that no PPD>5mm was present	Y; mechanical debridement of teeth and implants using hand instruments or ultrasonic devices as designed either for teeth or implants + OHI	Full mouth plaque scores obtained with the help of an erythrosine dye, Re-instruction in OH procedures as deemed necessary. All existing teeth and implants were cleaned using a rubber cup and a low-abrasive paste. SPC started at 6 weeks after surgery and then every 3 months. If BOP was detected during the maintenance visit, the area was re-instrumented with curettes	5 years	Recon 1: Implamed 1, Nobel biocare 17, Straumann 2, Ti-Unite 2; Recon 2: 2 Implamed, 17 Nobel biocare, 2 Straumann, 1 Ti-Unite, 1 unknown Recon 1: microrough (22); Recon 2: microrough (22), unknown (1)	NI	NI
(Polymeri et al., 2020)	RCT; Netherlands	University/ Hospital; Industry (Zimmer Biomet)	marginal bone loss ≥3mm detected radiographically and PPD ≥5mm at one or more peri-implant sites, in	24/1	Recon 1: 65.5±11.2; 5/6; Recon 2: 57.3±15.1; 8/5	Recon 1: 3S/8NS; Recon 2: 2S/11NS / diabetes mellitus (hemoglobin A1c ≥6.5%), use of corticosteroids or other anti-inflammatory prescription drugs were exclusion criteria	Recon 1: 4 (5 no history, 2 unknown); Recon 2: 6 (7 no history, 0 unknown)	Y, no details	Supragingival debridement and polishing with a rubber cup and a low-abrasive paste at 3,6,9, 12 months and OHI as necessary.	12 months	Recon 1: Biomet 3i (1), Frialit (1), MIS (1), Nobel/Branemark (2), Straumann (3), ICX 1, BioComp (1), Unknown (1); Recon 2: Astra (1), Biohorizon (1), Biomet 3i (4),	11 cement retained single crown, 7 cement retained FPD/splinted crowns, 5 screw-retained single	Recon 1: 7.0±3.4 years; Recon 2: 8.1±4.9 years

			combination with BoP/SoP								Nobel/Branemark (4), Straumann (4) / Recon 1: Micro-rough (8) – hydrophobic (5), unclear (3). Unclear type of surface (3) Recon 2: Micro-rough (9) – hydrophobic (5), unclear (4). Unclear type of surface (4)	crowns, 1 overdenture	
(Rakasevic and Gabric, 2021)	RCT; Serbia	University and Medical military Academy; partly supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia	> 1 year one or more endoosseus titanium implants with PPD> 5mm with BOP/SUP and radiographic bone loss. When possible previous radiographs were used, in absence of that 2mm bone loss was chosen as threshold	40/0	58.8+9.4; 64%/36%	NI / uncontrolled medical conditions, use of anti-inflammatory drugs in the previous six months were exclusion criteria	14	Y, mechanical debridement and OHI 2 weeks before surgery	NI	12 months	Zimmer MTX (7); Astra Tech Osseospeed (11); Nobel Biocare TiUnite (21); BCT (13)/ Polished (13). Micro-rough (39) – all hydrophobic	Single crown cement retained (12); implant-supported fixed denture cement-retained (33); overdenture (7)	7.01+3.52 years
(Gonzalez Regueiro et al., 2021)	Prospective case series; Spain	University/Hospital; no funding	PPD > 5 mm, BoP and/or SoP, and radiographic bone loss ≥3 mm	43/0	60.2±9.3; 15/28	22S/21N / immunosupressed patients, patients in treatment with corticosteroids in the past 12 months, patients in treatment with anticoagulants, acetylsalicylic acid and bisphosphonates, with signs of dysplasia or	Unclear, but untreated periodontitis was an exclusion criterion	Y, 1 week before surgery subgingival irrigation with a solution of piperacillin/tazobactam 100/12.5 was applied inside the peri-	Supragingival plaque removal using Teflon curettes at 3, 6 and 12 months	12 months	38 BioHorizons RBT and 5 Phibo TSA / All micro-rough - hydrophobic	screw-retained	7.8±3.7 years

						precancerous lesions were excluded		implant pocket					
(Regidor et al., 2022)	RCT; Spain	Private practice; self-funded by Arrow Development SL; biomaterials donated by Geistlich AG	PPD ≥7 mm, BOP and/or SOP and radiographically confirmed bone loss of ≥3 mm	39/4	61.1±9.6; 19/24 (Recon 1: 62.2±10.2; 8/14. Recon 2: 60±9; 11/10)	61.1±9.6; 19/24 (Recon 1: 62.2±10.2; 8/14.; Recon 2: 60±9; 11/10). Smokers of ≥10 cigarettes a day were excluded / Systemic diseases presenting as contraindications for oral surgical treatment (e.g., recent myocardial infarction, active treatment of malignancy, uncontrolled diabetes, radiotherapy of the head or neck within the last 5 years etc.), pregnant or nursing, allergy to collagen or if currently using medications such as analgesics/anti-inflammatory nonsteroidal drugs, immune-suppressive drugs (e.g., corticosteroids) or bisphosphonates were exclusion criteria	Unclear, but untreated periodontitis was an exclusion criterion	Y, supra and sub marginal instrumentation with a combination of plastic ultrasonic scalers and air-polishing with erythritol powder containing 0.3% chlorhexidine performed approximately 1 month before surgery	OHI, professional plaque removal using plastic ultrasonic scalers and air-polishing with erythritol every 6 months by a hygienist*	12 months	Recon 1: Straumann (18), unclear (4); Recon 2: Straumann (13), Astra Tech (1), unclear (7) / Recon 1: micro-rough (18) , unclear type of surface (4); Recon 2: microrough (14), unclear type of surface (7)	Screw-retained: 25; cemented: 18	11±4.9 years (Recon 1: 11.5±5.2; Recon 2: 10.4±4.5)

*Reclassified as the authors defined it as a cohort study; £ Authors provided the data for healthy patients (diabetic patients included in the original publication were not considered); Ψ information provided by the authors

Table 1 Demographics and main characteristics of the included studies. Recon, reconstructive surgery; AFS, access flap surgery; NST, non-surgical therapy; SPC, supportive periodontal care; SOP, suppuration; BOP, bleeding on probing; PPD, probing pocket depth; OHI, oral hygiene instructions; GDP, general dental practitioner

Study	Characteristics of treated sites	Was prosthesis removed? (Y/N/NI)	Healing protocol; use of antimicrobials (Y/N/NI; dosage)	Access flap surgery		Reconstructive surgery			
				N implants/N patients with outcomes	Implant decontamination/ implantoplasty (Y/N/NI)	N implants/N patients with outcomes	Implant decontamination/ implantoplasty (Y/N/NI)	Biomaterials employed (barrier, graft, bioactive factor)	Membrane stabilization
(Renvert et al., 2018b)	crater-like defect ≥3 mm as assessed from intra-oral radiographs. 23/41 (56.1%) three-wall defects, and 18/41 (43.9%) four wall defects	NI but from photos it looks like at least in some cases it was removed	Unclear, they mention full wound closure but they do not mention a second stage surgery to expose the implant	20/20	Soft tissues with evidence of chronic inflammation and mineralized deposits at implants were removed using titanium curettes. The implant surfaces were decontamination with 3% hydrogen peroxide cotton pellets, and implants were rinsed with a saline solution (2 × 20 ml)/ N	21/21	Same as AFS	DBBM granules (Endobon®, particle size 500–1000 µm) (Zimmer Biomet, Palm Beach Gardens, FL, USA) mixed with the subject's blood	N/A
(Isehed et al., 2018, Isehed et al., 2016)	Angular peri-implant bone loss ≥3 mm measured on x-ray. Vertical defect: median 6 mm (min-max 4-9 mm) (Recon), median 6 mm (min-max 4-9 mm) (AFS); number of osseous walls: median 3 (min-max 2-4) (Recon), median 2 (min-max 2-4) (AFS)	Y	Unsubmerged	13/13 at 12 months, 7/7 at 3 years, 5/5 at 5 years	implants were cleaned with an ultrasonic cleaner with a special implant tip and titanium instruments. Subsequently, cotton gauze and super floss cleaning was performed followed by rinsing with sodium chloride solution (9 mg/ml, 2 X 20 ml)/N	12/12 at 12 months, 11/11 at 3 years, 9/9 at 5 years	Same as AFS	0.3 ml EMD (Emdogain) applied on the implant from the bottom of the bone defect.	N/A
(Wohlfahrt et al., 2012, Andersen et al., 2017)	infrabony defects ≥4 mm, as verified during surgery, were included. Recon 1: surgical intrabony defect depth 6.8±2.7, defect width 2.6±0.6, no. of walls 2/3/1+2/2+3 = 3/2/4/7, defect angle 23.1±10.4; AFS: surgical intrabony defect depth 6.8±3.9, defect width 2.8±1.1, no. of walls 2/3/1+2/2+3 = 8/2/5/1, defect angle 24.5±9.6	Y	Submerged; 500mg amoxicillin TID, 400mg metronidazole bid 3 days pre-surgery and 7 days post-surgery	16/16 at 12 months, 6/6 at 7 years	Interior screw hole cleaned with 3% hydrogen peroxide and implant curetted with area-specific titanium curettes. Implant surfaces were conditioned with 24% EDTA for 2 minutes and rinsed with sterile saline / N	16/16 at 12 months, 6/6 at 7 years	Same as AFS	Titanium granules (Natix, Tigran Technologies AB)	N/A

(Jepsen et al., 2016)	intraosseous defect component ≥3 mm at the deepest point, 3 to 4 walls, defect with ≥ 270° (circumferential), and a defect angle ≤35° (from the axis of the implant). Vertical depth: 4.64±1.95 mesial and 4.63±2.26 distal (Recon); 3.98±2.50 mesial and 3.79±1.75 distal (AFS)	NI	Unsubmerged; amoxicillin 500 mg TID and metronidazole 400 mg BID for 8 days, starting 1 day before surgery	26/26	Granulation tissue removed using titanium curettes, and the exposed implant surfaces were cleaned mechanically by using a rotary titanium brush and decontaminated chemically with 3% hydrogen peroxide for 1 min, followed by rinsing with saline for 60 s (2 × 20 ml) / N	33/33	Same as AFS	Titanium granules (Tigran Technologies AB)	N/A
(Emanuel et al., 2020)	radiographic evidence of ≥2mm of intrabony defect, ≥ 2mm of bone at implant apex and ≥2mm distance to adjacent implants/teeth	NI	NI	13/13	Granulation tissue removed and the implant surface decontaminated with ultrasonic, sonic or hand instruments and implants rinsed with 30mL of sterile saline / N	14/14	Same as AFS	Biodegradable prolonged release local doxycycline formulated with beta-tricalcium phosphate graft (D-PLEX$_{500}$)	N/A
(Renvert et al., 2021)	≥3 bony walls, a verified intra-osseous component ≥ 3 mm during surgery; a circumference ≥270°. Recon: defect depth 5.0±1.7, defect width 2.7±0.5, 360° circumference 24 (65%), 270° circumference 13 (35%) ; AFS: defect depth 5.5±1.5, defect width 2.8±0.8, 360° circumference 20 (59%), 270° circumference 14 (41%)	For screw-retained restorations only	Unsubmerged; azithromycin: 500 mg on day 1 and 250 mg for 4 days	32/32	The inflammatory tissue was removed using titanium curettes and a rotary titanium brush. The implant surface was decontaminated using 3% hydrogen peroxide for 1 min, followed by rinsing with saline (2X20 ml) / N	34/34	Same as AFS	DBBM (Bio-Oss, Geistlich Pharma AG)) mixed with the subject's blood and native bilayer collagen membrane (Bio-gide, Geistlich Pharma AG)	NI
(Derks et al., 2022)[£]	circumferential and ≥3 mm deep. Configuration: open at buccal and lingual aspect (55); open at either bucccal or lingual aspect (51); contained (36); Buccal bone wall: intact (67); partially missing (31); missing (44)	Whenever possible (68.7%)	Unsubmerged; 10-day antibiotic regimen (Amoxicillin 750 mg bid) was initiated three days prior to surgery	68/64	Implant surfaces were cleaned by titanium curettes and a rotating titanium brush used at ≤1,200 rpm under continuous irrigation with saline/ N	70/64	Same as AFS	DBBM with 10% collagen (Bio-oss collagen, Geistlich Pharma AG)	N/A

Table 2 Characteristics of the interventions performed in the studies included for FQ1. DBBM, deproteinized bovine bone mineral; EMD, enamel matrix derivative; Recon, reconstructive surgery; AFS, access flap surgery

Study	Characteristics of treated sites	Was prosthesis removed? (Y/N/NI)	Healing protocol; use of antimicrobials (Y/N/NI; dosage)	Reconstructive surgery 1				Reconstructive surgery 2			
				N implants/N patients with outcomes	Biomaterials employed (barrier, graft, bioactive factor)	Membrane stabilization	Implant decontamination/ implantoplasty (Y/N/NI)	N implants/N patients with outcomes	Biomaterials employed (barrier, graft, bioactive factor)	Membrane stabilization	Implant decontamination/ implantoplasty (Y/N/NI)
Roos-Jansåker et al., 2014, Roos-Jansaker et al., 2011, Roos-Jansaker et al., 2007)	One-wall defects: 14.6%, 2-wall defects: 29.2%; 3-wall defects: 43.8%; circumferential defects: 10.4%; not classified: 2.1%	Y	Unsubmerged; Y amoxicillin (375mgX3) in combination with metronidazole (400mgX2), for 10 days. The antibiotic therapy was initiated the day before surgery. In cases of allergy to penicillin, Clindamycin (300mg) two times a day was prescribed.	29/17 at 12 months, 29/17 at 3 years, 23/13 at 5 years	Algipore, Friadent (natural occurring hydroxyapatite derived from calcifying maritime algae) mixed with blood + synthetic resorbable membrane (Osseoquest, WL Gore and Associates)	NI (the membrane was punched and trimmed to cover the defect completely)	All granulomatous tissue was carefully removed in the bone defect with titanium instruments. The threads were carefully cleaned from mineralized calculus and the implant surface was cleansed using hydrogen peroxide (3%), followed by profuse rinsing with saline/ N	36/19 at 12 months, 27/15 at 3 years, 22/12 at 5 years	Algipore, Friadent (natural occurring hydroxyapatite derived from calcifying maritime algae) mixed with blood	N/A	Same as Recon 1
(Aghazadeh et al., 2020, Aghazadeh et al., 2012)	angular peri implant bone defects ≥3mm in depth as determined from intra-oral radiographs and with ≥2 bone walls. Mean defect depth 2.5±1.3 mm (Recon 1) and 2.6±1.5 mm (Recon 2)	NI, but from the photos it seems like at least in some cases it was removed	Unsubmerged; Y azithromycin, 2 X 250 mg day 1 and 1 X 250 mg days 2–4	36/22	Autologous bone that was obtained from the subject using a bone scraper, using cortical bone. Bone was harvested from the surgical area or if this was not possible from the mandibular ramus region or the chin + resorbable collagen membrane (OsseoGuard®; Biomet3I)	NI	All granulomatous tissue was carefully removed with titanium instruments. The threads were carefully cleaned from mineralized calculus, if apparent, and the implant surface was cleaned with 3% hydrogen peroxide for 1 min., followed by profuse rinsing with saline/ N	39/23	DBBM (Bio-Oss particle size 0.25 μm; Geistlich Pharma) + resorbable collagen membrane (OsseoGuard®; Biomet3I Inc., Palm Beach, FL, USA)	NI	Same as Recon 1
(Froum et al., 2015)	peri-implant bone loss ≥3mm	NI but from photos in	Unsubmerged; amoxicillin 2000 mg or	170/100	EMD or PDGF applied to the decontaminated	NI	Thorough debridement of the osseous defect and implant surface using graphite curette				

		some it was removed and in some it was not	clindamycin 600mg 1 hour before the surgery. Afterwards, amoxicillin 500mg tid or clindamycin 150 mg qid for 10 days.		implant, then defects filled with DBBM (Bio-Oss, Geistlich Pharma AG) or bone allograft (Puros, Zimmer) which had been hydrated with PDGF at least 5 minutes prior to graft placement. When KT <2 mm, a sCTG was used as barrier to contain the biologic material. In cases of KT≥2mm, an absorbable collagen membrane (Bio-Gide, Geistlich; Ossix, OraPharma or Mucograft, Osteohealth) replaced the sCTG		or titanium tips followed by decontamination consisting in six steps: application of fine bicarbonate powder for 60 seconds using an air-abrasive device with a special contra-angled tip; 60-ec irrigation with sterile saline; application of tetracycline 50 mg/ml or minocycline 50mg/ml with cotton pellets or a brush (30 sec); second exposure to bicarbonate air abrasion (60 sec); application of 0.12% CHX gluconate with cotton pellets soaked in the solution (30-45 sec) or with a dedicated brush; 60 to 90 second re-irrigation with sterile saline / N				
(Roccuzzo et al., 2016, Roccuzzo et al., 2021)	9 Ia, 22 Ib, 14 Ic, 13 Id, 13 Ie	NI, but from photos it looks like they did not	Unsubmerged ; 1g of amoxicillin and clavulanic acid bid for 6 days, starting at least 1 h prior to surgery.	71/71 at 12 months, 51/51 at 5 years	DBBM with 10% collagen (Bio-oss collagen, Geistlich Pharma AG)	N/A	Implant surfaces were thoroughly debrided using titanium curettes. Whenever necessary, especially in deep narrow defects, the implant surfaces were instrumented with a titanium brush at 300 rpm under irrigation. Implant surface was treated with EDTA 24% for 2 min and CHX 1% gel for 2 min. Then the implant and bony surfaces were thoroughly rinsed with sterile physiologic saline / N				
(Isler et al., 2018, Isler et al., 2022)	infrabony defect ≥3 mm, with PPD ≥5 mm with BOP and/or SOP. For the 51 patients with 3-year data: 22 2-wall defects (11 Recon 1, 11 Recon 2); 12 3-wall defects (5	Y	Submerged; amoxicillin 500 mg + metronidazole 500 mg tid for 1 week	26/26 at 12 months, 25/25 at 3 years	DBBM (Bio-Oss, Geistlich Pharma AG) and two pieces of concentrated growth factor membrane	No fixation	Implant surfaces were cleaned using titanium curettes and saline-soaked cotton gauzes / N	26/26 at 12 months and 3 years	DBBM (Bio-Oss, Geistlich Pharma AG) and native bilayer collagen membrane (Bio-gide, Geistlich Pharma AG)	No fixation	Same as Recon 1

	Recon 1, 7 Recon 2); 17 4-wall defects (9 Recon 1, 8 Recon 2)										
(La Monaca et al., 2018)	bone loss of ≥3 mm detected on standard intraoral radiographs	Y	Unsubmerged ; 875 mg of amoxicillin plus 125 mg of clavulanic acid bid and 250 mg of metronidazole tid for 10 days, starting 1 hr before surgery.	34/34	Mineralized dehydrated bone allograft (Puros®; Zimmer Dental) and native bilayer collagen membrane (Bio-gide, Geistlich Pharma AG)	No fixation (to ensure the stability of the graft material, the membrane which had been trimmed to the appropriate size and shape to cover the entire defect plus 2–3 mm of the surrounding bone was adapted around the implant neck)	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 chemically 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 / N				
(Mercado et al., 2018)	"crater-like" or circumferential defect, a BOP/SOP pocket of >4 mm, ≥20% alveolar bone loss	NI but from phots it looks like it was not	NI, but from photos it looks it was unsubmerged; Incorporated with graft material (100mg doxycycline)	30/30	DBBM with 10% collagen (Bio-oss collagen, Geistlich Pharma AG) mixed with 0.35 ml of EMD for 15 min. One capsule of doxycycline 100 mg was added to the DBBM and EMD and mixed until a homogenous material was formed	N/A	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 / N				
(Polymeri et al., 2020)	intra-osseous defect component ≥3 mm at the deepest part and presence of at least 3 osseous walls.	Whenever possible	Unsubmerged ; amoxicillin 500 mg tid and metronidazole 500 mg bid for 8 days, starting one	11/11	DBBM (Bio-Oss, Geistlich Pharma AG)	N/A	Granulation tissue was removed with titanium curettes, and the exposed implant threads were carefully debrided and decontaminated with 3% hydrogen peroxide for 1 min, followed by rinsing with copious amounts of saline / N	13/13	bovine-derived hydroxyapatite ceramic with small granule size (particle size 500–1,000 μm) (Endobon,	N/A	Same as Recon 1

			day before the surgery.						Zimmer Biomet)		
(Rakasevic and Gabric, 2021)	Class 1b: 21 (41%); Class 1d: 17 (32%); Class 1e: 14 (27%)	Whenever possible and needed	Unsubmerged; amoxicillin 500 mg tid per day for 5 days	26/21	DBBM (Bio-Oss, Geistlich Pharma AG) and native bilayer collagen membrane (Bio-gide, Geistlich Pharma AG)	NI	Mechanical implant surface cleaning was done using graphite curettes, then decontamination was performed using PDT. Photosensitizer, phenothiazine chloride was applied onto implant surface, bone and peri-implant soft tissue, for 3 minutes. Irrigation of photosensitizer was performed with saline. Implant surface and the surrounding tissue were exposed to the laser light by means of fibers for 30 seconds/spot, which operates on wavelength of 660 nm and irradiance of 100 mW / N	25/19	Same as Recon 1	NI	Mechanical implant surface cleaning were done using graphite curettes. Then 1% gel of CHX was put on implant surface. One minute after exposing implant surface with CHX, it was irrigated for 1 minute by saline / N
(Gonzalez Fregueiro et al., 2021)	type 1b: 31 (72.1%); type 3b/c: 12 (27.9%)	Y	Unsubmerged; no systemic antibiotic but local application of piperacillin/tazobactam antibiotic	43/43	Hydroxyapatite bone substitute with a particle size of 250–1000 μm (Osbone, Curasan) that was hydrated with piperacillin/tazobact 100/12.5 mg and compacted into the defect and resorbable collagen membrane (Osgide, Curasan)	titanium tacks	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 washed out with sterile saline solution, and the implant surface was scrubbed with gauze impregnated with piperacillin/tazobactam for 1 min / Y (implantoplasty performed at the supra-osseous component of the defect and at the buccal and/or lingual dehiscences using large, medium, and fine diamond drills)				
(Regidor et al., 2022)	Peri-implant intra-bony defect with a depth of ≥3 mm, confirmed intrasurgically (no minimum number of bony walls	Whenever possible (72.7%)	Unsubmerged; amoxicillin 750 mg bid for 10 days was prescribed since 3 days	20/20	DBBM with 10% collagen (Bio-oss collagen, Geistlich Pharma AG)	N/A	Implant surfaces were cleaned by titanium curettes and a rotating titanium brush used at ≤1,200 rpm under continuous irrigation with saline / N	19/19	DBBM with 10% collagen (Bio-oss collagen, Geistlich Pharma AG) and native	The membrane was customized to fully cover the peri-	Same as Recon 1

	required). Bone crest to the bottom of the defect: 5.2±1.6 (Recon 1); 6.4±2.5 (Recon 2); implant shoulder to bottom of the defect: 6.7±2.1 (Recon 1); 7.9±2.8 (Recon 2); Width: 2.6±1.6 (Recon 1); 3.1±2.2 (Recon 2); Configuration: open at either bucccal or lingual aspect (29); contained (14); Buccal bone wall: intact (12); partially missing (16); missing (15)		before surgery						bilayer collagen membrane (Bio-gide, Geistlich Pharma AG)	implant defect and bone substitute material and was then stabilized by ≥1 fixing pin	

Table 3 Characteristics of the interventions performed in the studies included for FQ2. PDGF, platelet-derived growth factor; Recon, reconstructive surgery; DBBM, deproteinized bovine bone mineral; EMD, enamel matrix derivative; KT, keratinized tissue; sCTG, subepithelial connective tissue graft; EDTA, ethylenediaminetetraacetic acid; PDT, photodynamic therapy; CHX, chlorhexidine