

Efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects. A systematic review and meta-analysis

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Abstract

Objectives: The present systematic review aimed at evaluating the efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects.

Methods: Studies reporting on outcomes of reconstructive surgery at peri-implantitis-related bone defects at 12 months were identified through an electronic search. Following data extraction, two different sets of meta-analyses were performed. Primarily, controlled studies were used to evaluate the potential benefit of reconstructive surgical therapy over controls. Secondly, overall outcome of reconstructive surgical therapy was assessed by comparing baseline values with outcomes at 12 months. Results were expressed as weighted mean differences (WMD) or risk ratios (RR). Heterogeneity was described by I^2 and prediction intervals.

Results: The potential benefit of reconstructive techniques over control procedures was evaluated in three studies, representing a total of 116 implants. Altogether, 16 studies reported on the outcome of reconstructive measures at 12 months after surgery. The meta-analyses identified a larger improvement in marginal bone levels (MBL, WMD = 1.7 mm) and in defect fill (WMD = 57%) for test procedures, but found no differences for clinical measures (reduction of probing depth (PD) and bleeding on probing (BOP)). Changes of clinical attachment and soft tissue levels were not considered. In terms of overall outcome, therapy resulted in improved MBL (WMD = 2.0 mm) and CAL (WMD = 1.8 mm), in recession (WMD = 0.7 mm), in reduced PD (WMD = 2.8 mm) and in reduced BOP (Implants: RR = 0.4/Sites: RR = 0.2). None of the included studies addressed patient-reported outcome measures.

Conclusions: The available evidence on reconstructive therapy at peri-implantitis-related defects is limited by (a) the low number of controlled studies, (b) the lack of controlled studies for commonly used procedures, (c) the heterogeneity between studies and (d) the choice of outcome measures. A high variability for predicted outcomes at 12 months was noted. The interpretation of the demonstrated larger MBL gain for test procedures is difficult as graft material may not be distinguishable from newly formed bone. Potential aesthetic and patient-reported advantages remain to be demonstrated.

KEYWORDS

bone regeneration, dental implant, peri-implantitis, reconstructive therapy

1 | INTRODUCTION

Peri-implantitis is a pathological condition occurring in tissues around dental implants. It is characterized by inflammation in the peri-implant connective tissue and progressive loss of supporting bone (Schwarz, Derks, Monje, & Wang, 2018). In a systematic review, a weighted mean patient prevalence of peri-implantitis of 22% was reported (Derks & Tomasi, 2015). The prevalence ranged from 1% to 47% in different reports, mainly due to the variation of case definitions among studies (Tomasi & Derks, 2012). It was suggested that peri-implantitis-associated bone loss was time-dependent and accelerated over time (Derks et al., 2016; Fransson et al., 2010).

The goal of peri-implantitis treatment is resolution of soft tissue inflammation and, subsequently, the prevention of further marginal bone loss. Non-surgical treatment modalities are frequently insufficient to achieve this objective (Faggion, Listl, Frühauf, Chang, & Tu, 2014; John, Becker, Schmucker, & Schwarz, 2017), while surgical procedures are considered more efficacious in the treatment of peri-implantitis (Faggion, Chambrone, Listl, & Tu, 2013; Lindhe & Meyle, 2008). The feasibility of a surgical approach has been extensively demonstrated in pre-clinical research (Albouy, Abrahamsson, Persson, & Berglundh, 2011; Carcuac, Abrahamsson, Charalampakis, & Berglundh, 2015; Persson, Araújo, Berglundh, Gröndahl, & Lindhe, 1999), and clinical efficacy has been documented in studies with substantial periods of follow-up (Berglundh, Wennström, & Lindhe, 2018; Rocuzzo, Pittoni, Rocuzzo, Charrier, & Dalmaso, 2017; Schwarz, John, Schmucker, Sahm, & Becker, 2017).

Outcomes of surgical therapy of peri-implantitis are reported to be influenced by implant surface characteristics (Carcuac et al., 2017; Rocuzzo et al., 2017) and by the configuration of the peri-implant bone defect (Schwarz, Sahm, Schwarz, & Becker, 2010). Bone defects associated with peri-implantitis commonly involve the whole circumference of the affected implant and have an angular outline on the mesial and distal aspects (Schwarz et al., 2007). Angular bone defects at teeth may have an overall different morphology, and studies have indicated that reconstructive techniques are successful in terms of clinical attachment gain and prevention of soft tissue recession (Reynolds et al., 2015). While the documentation of reconstructive surgery in the periodontal literature is extensive, evidence on its use at peri-implantitis sites is only emerging. The aim of the present systematic review was to evaluate the efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects.

2 | MATERIALS AND METHODS

2.1 | Protocol and eligibility

Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were considered (Moher, Liberati, Tetzlaff, & Altman, 2009), and the protocol was registered at Prospero (CRD42018089236). The focused question of this

Clinical Relevance

Scientific rationale for review: Peri-implantitis is a common complication in patients provided with implant-supported restorative therapy, and treatment commonly requires surgical access. *Principal findings:* Evidence on reconstructive therapy at peri-implantitis-related bone defects is limited. A benefit for reconstructive techniques over control procedures was observed for radiographic outcomes only. *Practical implications:* Clinicians should be aware of the lack of evidence suggesting improved aesthetic or patient-reported outcomes following reconstructive therapy at peri-implantitis-related bone defects.

systematic review was: What is the benefit of using a reconstructive technique as adjunct to surgical therapy of peri-implantitis?

2.2 | Inclusion criteria (PICOS)

2.2.1 | Population

Patients in good general health requiring treatment of peri-implantitis.

2.2.2 | Intervention

Reconstructive technique as adjunction to surgical therapy of peri-implantitis.

2.2.3 | Comparison

Surgical therapy of peri-implantitis alone (open-flap debridement).

2.2.4 | Outcomes

Changes of radiographic marginal bone level, clinical attachment level and soft tissue level. Reduction of probing depth and peri-implant bleeding on probing. Implant survival (in studies with a follow-up of ≥ 5 years).

2.2.5 | Study design

Randomized clinical trials (RCT), controlled clinical trials or prospective case series with at least 12 months of follow-up with a minimum of 10 patients (5 per group in controlled studies).

2.3 | Exclusion criteria

- Pre-clinical studies.
- Surgical therapy of peri-implantitis applying pocket elimination.
- Articles published in languages other than English.

2.4 | Interventions and comparisons

Studies on reconstructive techniques in the surgical therapy of peri-implantitis were considered. The following procedures and possible combinations were accepted: (a) bone grafting (autologous, allogeneic or xenogeneic); (b) guided bone regeneration; and (c) use of biological agents/growth factors.

Primarily, the outcomes of reconstructive therapy were compared to results after identical surgical interventions omitting the reconstructive technique (control: open-flap debridement). In a second step, the overall outcome of reconstructive therapy was evaluated by comparing pre-surgical findings with outcomes at 12 months.

2.5 | Outcome measures

Outcomes at 12 months following surgical therapy of peri-implantitis were extracted. The primary outcome was change of radiographic marginal bone level (MBL) expressed in mm. We further considered fill of the bone defect expressed as a percentage. Additional secondary outcomes were changes of clinical attachment level (CAL), changes of soft tissue level (REC), changes of bleeding on probing (BOP), changes of suppuration on probing (SUP) and changes of probing depth (PD). Combinations of outcomes, that is composite outcomes (absence of additional bone loss, absence of inflammation and shallow probing), and patient-reported outcome measures (PROMs) were also considered. Implant survival was assessed in studies with a follow-up of ≥ 5 years.

2.6 | Search strategy

Three electronic databases were searched for relevant articles in February 2018 using the following search algorithms.

2.6.1 | MEDLINE via PubMed (2018-02-20)

(peri-implantitis OR periimplantitis OR peri implantitis) AND (surgical treatment OR surgery OR surgical OR reconstructive OR regenerative OR regeneration) NOT (retrospective OR review OR in vitro OR case report OR orthopedic OR animal OR experimental)

Filter: English

2.6.2 | Web of science (2018-02-20)

((peri-implantitis OR periimplantitis OR peri implantitis) AND (surgical treatment OR surgery OR surgical OR reconstructive OR regenerative OR regeneration))

Refined by: WEB OF SCIENCE CATEGORIES: (DENTISTRY ORAL SURGERY MEDICINE) AND DOCUMENT TYPES: (ARTICLE) AND LANGUAGES: (ENGLISH)

2.6.3 | Cochrane central register of controlled trials (2018-02-20)

(peri-implantitis OR periimplantitis OR peri implantitis) AND (surgical treatment OR surgery OR surgical OR reconstructive OR regenerative OR regeneration)

In addition, a hand search was performed including reference lists and previous systematic reviews. Titles of all identified articles were screened for eligibility. Abstracts were then studied and selected independently by two reviewers (CT & JD). Relevant articles were analysed in full text and, again, independently selected for inclusion. The level of agreement for the two selections was expressed by *k*-scores. Disagreement was resolved by discussion.

2.7 | Data extraction

Two reviewers (ER & JD) extracted data from included articles and entered relevant information into pre-defined evidence tables. Studies were sorted according to design (controlled studies vs. studies without controls), and outcomes at 12 months were illustrated for all study arms. For controlled studies, potential benefits of test procedures were highlighted. We specifically focused on inclusion and exclusion criteria for each of the study samples in order to evaluate potential heterogeneity among the sampled populations. In case of missing data/information, authors were contacted.

2.8 | Quality assessment

One reviewer (AOV) assessed the risk of bias for included studies. For randomized trials, criteria described in the Cochrane Handbook (Higgins et al., 2011) were used. In six categories (sequence generation, allocation concealment, detection bias, attrition bias, selective reporting bias and other potential risk of bias), a rating of low, unclear or high risk of bias was performed.

For studies lacking controls, that is observational studies, risk of bias was assessed using a modified version of the Newcastle-Ottawa Scale for cohort studies (Wells et al., 2014). Thus, five items (representativeness of cohort, ascertainment of exposure, outcome at start of study, comparability of cohorts and assessment of outcome) were scored as present, not present or not applicable.

2.9 | Risk of bias across studies

The publication bias was evaluated using funnel plots for the outcomes: (a) changes of MBL and (b) PD reduction. A sensitivity analysis of the meta-analysis results was also performed, if plausible, by selectively excluding studies from the different analyses.

2.10 | Data analysis

For continuous outcomes at 12 months (changes of MBL, defect fill, CAL, REC and PD), mean values and standard deviations were pooled

and analysed with weighted mean differences (WMD) and 95% confidence intervals (CIs). For dichotomous data (BOP), the estimates of the effect were expressed as risk ratios (RR) and 95% CIs. Study-specific estimates were pooled with both the fixed- and random-effects models (DerSimonian & Laird, 1986), and the random-effects model results were presented.

We performed two different sets of analyses. Primarily, controlled studies were used to evaluate the potential benefit of reconstructive surgical therapy. For this analysis, no distinction was made between the different surgical techniques. Open-flap debridement was considered as control. Secondly, the outcome of reconstructive

surgical therapy was assessed by comparing baseline values with outcomes at 12 months. In this analysis, controlled studies and studies without controls were included. For studies with multiple arms, each reconstructive intervention was considered separately. Further, sensitivity analysis was performed by considering studies with and without controls separately.

Statistical heterogeneity among studies was explored by the I^2 index (Higgins, Thompson, Deeks, & Altman, 2003) and Cochrane's Q statistic ($p < 0.1$). Forest plots were used to illustrate the outcomes of the analyses. Results were combined with random-effects meta-analysis, reporting tau-squared (between studies variance

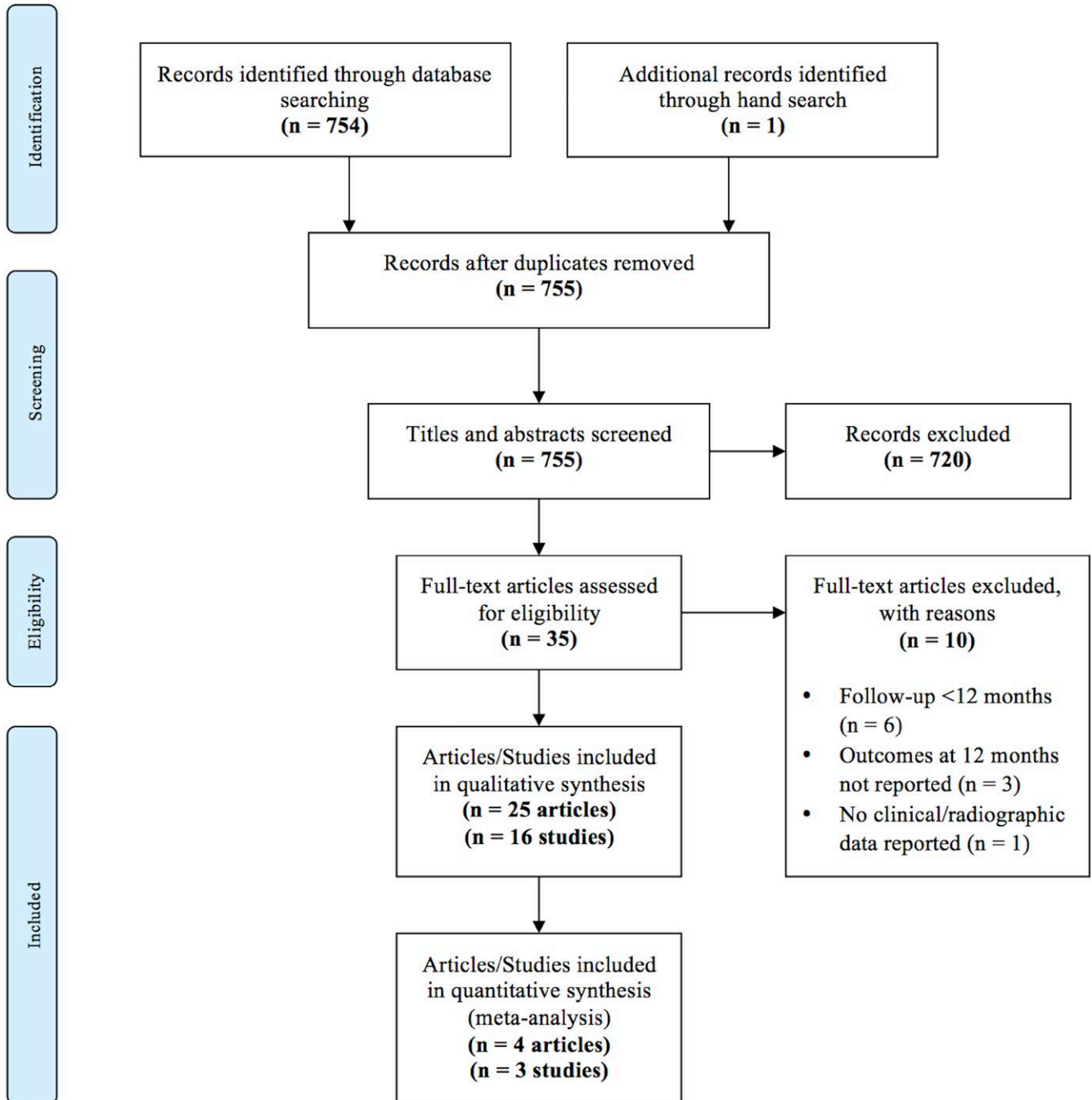


FIGURE 1 PRISMA flow diagram depicting the selection process

TABLE 1 Included studies: Outcomes reported in controlled studies ($n = 4$ articles, $n = 3$ studies)

Study	Arms	Number of observations at 12 months	Outcomes at 12 months	Benefit of test procedure at 12 months	Comments
Isehede et al. (2016)	Open-flap debridement	13 patients	Δ MBL: -0.2 ± 1.1 mm	Δ MBL: 0.5 mm	Mean Δ MBL and Δ PD kindly provided by the authors. BOP/SUP positive if present at any site of implant. REC and PROMs not reported. No systemic antibiotics prescribed.
		13 implants	Δ PD: -4.0 ± 2.9 mm Δ BOP% (implants): -20 Δ SUP% (implants): -36	Δ PD: 1.5 mm (in favour of control group) Δ BOP% (implants): 0 Δ SUP% (implants): 17	
Jepsen et al. (2016)	Open-flap debridement	12 patients	Δ MBL: -0.7 ± 1.1 mm	Δ MBL: 2.6 mm (mesial), 2.7 mm (distal)	Composite outcome (BOP-, PD < 5 mm and absence of additional bone loss) Control: 23.0% of implants Test: 30.3% of implants BOP% based on 6 sites/implant. BOP/SUP positive if present at any site of implant. REC and PROMs not reported. Systemic antibiotics prescribed
		12 implants	Δ PD: -2.5 ± 2.0 mm Δ BOP% (implants): -20 Δ SUP% (implants): -53	%Defect fill: 55.9 (mesial), 52.3 (distal) Δ PD: 0.2 mm Δ BOP% (sites): 11.2 Δ BOP% (implants): 0 Δ SUP% (implants): 2.4 (in favour of control group)	
Wohlfahrt et al. (2012) 12 months	Open-flap debridement	26 patients	Δ MBL: -1.0 ± 1.4 mm (mesial), -0.8 ± 1.1 mm (distal)	Δ MBL: 1.9 mm	BOP expressed as mean number of positive sites (out of 6) per implant. SUP, REC and PROMs not reported. Systemic antibiotics prescribed.
		26 implants	%Defect fill: 23.1 \pm 46.3 (mesial), 21.9 \pm 30.2 (distal) Δ PD: -2.6 ± 1.4 mm Δ BOP% (sites): -44.9 ± 38.2 Δ BOP% (implants): -30.8 Δ SUP% (implants): -25.6 ± 32.7	Δ PD: 0.3 mm (in favour of control group) Δ BOP (sites): 0.18 (in favour of control group)	
also reported in: Andersen et al. (2017) 7 years	Porous titanium granules	33 patients	Δ MBL: -3.6 ± 2.1 mm (mesial), -3.5 ± 2.2 mm (distal)	Δ BOP (sites): 0.18 (in favour of control group)	Submerged healing for 6 months following surgery. 17/32 patients attended the 7-year examination: 3 implants in 3 patients (all in the test group) were lost during follow-up.
		33 implants	%Defect fill: 79.0 \pm 29.9 (mesial), 74.2 \pm 36.3 (distal) Δ PD: -2.8 ± 1.3 mm Δ BOP% (sites): -56.1 ± 30.5 Δ BOP% (implants): -30.3 Δ SUP% (implants): -23.2 ± 32.8	Δ PD: 0.18 (in favour of control group)	
Wohlfahrt et al. (2012) 12 months	Open-flap debridement	16 patients 16 implants	Δ MBL: -0.1 ± 1.9 mm %Defect fill: -14.8 ± 83.4 Δ PD: -2.0 ± 2.3 mm Δ BOP (sites): -0.56 ± 2.9	Δ MBL: 1.9 mm %Defect fill: 71.8 Δ PD: 0.3 mm (in favour of control group)	BOP expressed as mean number of positive sites (out of 6) per implant. SUP, REC and PROMs not reported. Systemic antibiotics prescribed.
also reported in: Andersen et al. (2017) 7 years	Porous titanium granules	16 patients 16 implants	Δ MBL: -2.0 ± 1.7 mm %Defect fill: 57.0 ± 45.1 Δ PD: -1.7 ± 1.7 mm Δ BOP (sites): -0.38 ± 2.1	Δ BOP (sites): 0.18 (in favour of control group)	Submerged healing for 6 months following surgery. 17/32 patients attended the 7-year examination: 3 implants in 3 patients (all in the test group) were lost during follow-up.

Note. BOP: bleeding on probing; MBL: marginal bone level; PD: probing depth; REC: soft tissue level; PROMs: patient-reported outcome measures; SUP: suppuration on probing.

TABLE 2 Included studies: Outcomes reported in studies without controls ($n = 21$ articles, $n = 13$ studies)

Study	Groups	Number of observations at 12 months	Outcomes at 12 months	Comments
Aghazadeh et al. (2012)	Group 1: Autologous bone graft (particulate), resorbable membrane Group 2: Bovine bone mineral (particles), resorbable membrane	22 patients 36 implants 23 patients 39 implants	Δ MBL: -0.2 mm (SE: 0.3) Δ PD: -2.0 mm (SE: 0.2) Δ BOP% (sites): -44.8 (SE: 6.3) Δ SUP% (sites): -11.5 (SE: 5.2) Δ MBL: -1.1 mm (SE: 0.3) Δ PD: -3.1 mm (SE: 0.2) Δ BOP% (sites): -50.4 (SE: 5.3) Δ SUP% (sites): -25.2 (SE: 4.2)	Composite outcome 1 (BOP+, PD <5 mm and absence of additional bone loss) Group 1: 11.1% of implants Group 2: 20.5% of implants Composite outcome 2 (BOP+ at ≤ 1 site, PD <5 mm and absence of additional bone loss) Group 1: 13.9% of implants Group 2: 38.5% of implants BOP/SUP% based on 4 sites/implant. REC and PROMs not reported. Systemic antibiotics prescribed
Behneke et al. (2000)	Autologous bone graft (block or particulate), supporting screws or fibrin glue	Number of patients not reported 18 implants	Δ MBL: -3.9 mm Δ PD: -2.7 mm Δ CAL: -2.2 mm	SE or SD of mean changes not reported. BOP, SUP, REC and PROMs not reported. Δ REC calculated: 0.5 mm Outcomes at 12 months reported for subsample. Systemic antibiotics prescribed.
Khoury and Buchmann (2001)	Group 1: Autologous bone graft (block and particulate) Group 2: Autologous bone graft (block and particulate), ePTFE membrane Group 3: Autologous bone graft (block and particulate), collagen membrane	7 patients 12 implants 11 patients 20 implants 7 patients 9 implants	Δ MBL: -2.4 mm Δ PD: -5.4 mm Δ Probing bone level: -2.4 mm Δ MBL: -3.3 mm Δ PD: -4.8 mm Δ Probing bone level: -3.7 mm Δ MBL: -2.5 mm Δ PD: -3.3 mm Δ Probing bone level: -2.5 mm	SE or SD of mean changes not reported. BOP, SUP, REC and PROMs not reported. Systemic antibiotics prescribed
Matarasso et al. (2014)	Bovine bone mineral (particles), collagen membrane	11 patients 11 implants	Δ MBL: -2.8 mm %Defect fill: 93.3 ± 13.0 Δ REC: -1.3 mm Δ PD: -4.1 mm Δ CAL: -3.0 mm Δ BOP% (sites): -13.6	SE or SD of mean changes not reported. BOP% based on 6 sites/implant. 6 of 11 implants free of BOP prior to surgery. SUP and PROMs not reported. Systemic antibiotics prescribed
Nart et al. (2017)	Allograft (impregnated with vancomycin and tobramycin), collagen membrane	13 patients 17 implants	Δ MBL: -3.6 mm %Defect fill: 87.0 ± 18.2 Δ REC: -1.3 ± 0.5 mm Δ PD: -4.2 ± 1.5 mm Δ BOP% (sites): -70.6 Δ SUP% (sites): -100.0	SE or SD of mean changes not reported for all outcomes. BOP/SUP% based on 6 sites/implant. PROMs not reported. No systemic antibiotics prescribed

(Continued)

TABLE 2 (Continued)

Study	Groups	Number of observations at 12 months	Outcomes at 12 months	Comments
Rocuzzo et al. (2011) 12 months also reported in: Rocuzzo et al. (2017) 7 years	Group 1: TPS implants Bovine bone mineral (block)	14 patients 14 implants	Δ MBL: -1.6 ± 0.7 mm Δ PD: -2.1 ± 1.2 mm Δ BOP% (sites): -33.9 Δ SUP% (implants): -60.0	BOP% based on 4 sites/implant. SUP expressed as % of implants demonstrating suppuration. REC and PROMs not reported. Systemic antibiotics prescribed. 24/26 patients attended the 7-year examination: 4 implants in 4 patients (2 in each group) were lost during follow-up
	Group 2: SLA implants Bovine bone mineral (block)	12 patients 12 implants	Δ MBL: -1.9 ± 1.3 mm Δ PD: -3.4 ± 1.7 mm Δ BOP% (sites): -60.4 Δ SUP% (implants): -100.0	
Rocuzzo et al. (2016)	Bovine bone mineral (block)	71 patients 71 implants	Δ PD: -2.9 ± 1.7 mm Δ BOP% (sites): -53.2 Δ SUP% (implants): -35.5	Composite outcome 1 (BOP- and PD ≤ 5 mm) 49.3% of implants Composite outcome 2 (BOP- and PD ≤ 6 mm) 56.0% of implants BOP% based on 4 sites/implants. SUP expressed as % of implants demonstrating suppuration. MBL, REC and PROMs not reported. Δ REC for different defect categories varied from 0.5 mm to 0.9 mm. Estimated mean: 0.69 ± 0.76 mm. Systemic antibiotics prescribed
Roos-Jansåker et al. (2007a)	Hydroxyapatite, resorbable membrane	12 patients 16 implants	Δ MBL: -2.3 ± 1.2 mm Δ REC: -2.8 ± 1.4 mm Δ PD: -4.2 ± 1.5 mm Δ CAL: -1.4 ± 1.7 mm Δ BOP% (implants): -62.5	BOP expressed as % of bleeding at deepest site of implant. SUP and PROMs not reported. Systemic antibiotics prescribed. Submerged healing for 6 months following surgery.
Roos-Jansåker et al. (2007b) 12 months also reported in: Roos-Jansåker, Lindahl, Persson, and Renvert (2011) 3 years Roos-Jansåker et al. (2014) 5 years	Group 1: Hydroxyapatite, resorbable membrane Group 2: Hydroxyapatite	17 patients 29 implants 19 patients 36 implants	Δ MBL: -1.5 ± 1.2 mm Δ REC: -1.3 ± 1.5 mm Δ PD: -2.9 ± 2.0 mm Δ CAL: -1.6 ± 2.0 mm Δ BOP% (sites): -57.7 Δ MBL: -1.4 ± 1.3 mm Δ REC: -1.6 ± 1.6 mm Δ PD: -3.4 ± 1.6 mm Δ CAL: -1.8 ± 1.4 mm Δ BOP% (sites): -67.9	BOP% based on 4 sites/implant. SUP and PROMs not reported. Systemic antibiotics prescribed. 25/38 patients attended the 5-year examination: no implants were lost during follow-up

(Continued)

TABLE 2 (Continued)

Study	Groups	Number of observations at 12 months	Outcomes at 12 months	Comments
Schwarz et al. (2008) 2 years also reported in: Schwarz, Bieling, Latz, Nuesry, and Becker (2006) 6 months Schwarz, Sahm, Bieling, and Becker (2009) 4 years	Group 1: Hydroxyapatite Group 2: Bovine bone mineral (particles), collagen membrane	9 patients 9 implants 11 patients 11 implants	Δ REC: -0.4 ± 0.2 mm Δ PD: -2.0 ± 0.5 mm Δ CAL: -1.6 ± 0.3 mm Δ BOP% (sites): -44 Δ REC: -0.3 ± 0.4 mm Δ PD: -2.7 ± 0.6 mm Δ CAL: -2.4 ± 0.7 mm Δ BOP% (sites): -49	BOP% based on 6 sites/implant. MBL, SUP and PROMs not reported. No systemic antibiotics prescribed
Schwarz et al. (2010)	Bovine bone mineral (particles), collagen membrane	27 patients 27 implants	Defect Class Ib (n = 9) Δ REC: -0.4 ± 0.7 mm Δ PD: -1.6 ± 0.9 mm Δ CAL: -1.2 ± 1.1 mm Δ BOP% (sites): -39.9 ± 16.6 Defect Class Ic (n = 9) Δ REC: -0.5 ± 0.5 mm Δ PD: -1.6 ± 0.7 mm Δ CAL: -1.1 ± 0.9 mm Δ BOP% (sites): -25.9 ± 14.7 Defect Class Ie (n = 9) Δ REC: -0.3 ± 0.6 mm Δ PD: -2.7 ± 0.7 mm Δ CAL: -2.4 ± 1.0 mm Δ BOP% (sites): -61.1 ± 16.7	BOP% based on 6 sites/implant. MBL, SUP and PROMs not reported. No systemic antibiotics prescribed
Schwarz et al. (2012) 2 years also reported in: Schwarz, Sahm, Iglhaut, and Becker (2011) 6 months Schwarz, Hegewald, John, Sahm, and Becker (2013) 4 years Schwarz et al. (2017) 7 years	Group 1: Implant surface decon- tamination with plastic curettes, cotton pellets and sterile saline Bovine bone mineral (particles), collagen membrane Group 2: Implant surface decon- tamination with Er:YAG laser Bovine bone mineral (particles), collagen membrane	14 patients 10 patients	Δ REC: -0.5 ± 0.4 mm Δ PD: -2.0 ± 1.6 mm Δ CAL: -1.5 ± 1.6 mm Δ BOP% (sites): -60.1 ± 26.6 Δ REC: -0.4 ± 0.2 mm Δ PD: -1.7 ± 1.2 mm Δ CAL: -1.3 ± 1.2 mm Δ BOP% (sites): -55.0 ± 28.4	BOP% based on 6 sites/implant. MBL, SUP and PROMs not reported. No systemic antibiotics prescribed. 15/32 patients attended the 7-year examination; 4 patients were excluded between years 2 and 3 due to severe re-infection. No information on implant loss
Wiltfang et al. (2012)	Autologous bone graft (particulate), xenogeneic bone graft	22 patients 36 implants	Δ Defect depth: -3.5 mm (95% CI: $-4.3/-2.7$) Δ REC: -1.3 mm Δ PD: -4.0 mm (95% CI: $-4.6/-3.3$) Δ BOP% (implants): -36 Δ SUP% (implants): -72	SE, SD or CI of mean changes not reported for all outcomes. BOP/SUP positive if present at any site of implant. 39% implants free of BOP prior to surgery. MBL and PROMs not reported. Systemic antibiotics prescribed.

Note. BOP: bleeding on probing; CAL: clinical attachment level; CI: confidence interval; MBL: marginal bone level; PD: probing depth; PROMs: patient-reported outcome measures; REC: soft tissue level; SUP: suppuration on probing; SE: standard error; SD: standard deviation.

included in the analysis), which was used to calculate prediction intervals (Borenstein, Higgins, Hedges, & Rothstein, 2017). Statistical significance was set to $p < 0.05$. All analyses were performed with Review Manager (RevMan version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3 | RESULTS

3.1 | Search

Results of the search are illustrated in Figure 1. The electronic search yielded 754 titles. One additional article (Hamzacebi, Oduncuoglu, & Alaaddinoglu, 2015) was identified through the hand search, rendering an initial selection of 755 records. Following screening of titles and abstracts, 35 articles were selected for full-text analysis ($\kappa = 0.86$). An additional 10 articles were excluded, resulting in a final selection of 25 articles describing 16 different studies. The reasons for exclusion are given in Table A-1. The agreement on the final selection was $\kappa = 0.87$.

3.2 | Description of selected studies

3.2.1 | Design

The included studies are described in Tables 1 and 2. Out of the 16 relevant studies, three included controls and were designed as randomized controlled trials (Ished et al., 2016; Jepsen et al., 2016; Wohlfahrt et al., 2012). Each study included one single experimental group, and open-flap debridement was provided to controls.

Of the 13 studies without controls, three were designed as randomized trials (Aghazadeh, Persson, & Renvert, 2012; Schwarz, John, Mainusch, Sahm, & Becker, 2012; Schwarz et al., 2008), while the remaining were observational studies. A total of four studies included multiple interventional arms (Aghazadeh et al., 2012; Khoury & Buchmann, 2001; Roos-Jansåker, Renvert, Lindahl, & Renvert, 2007b; Schwarz et al., 2008), comparing different reconstructive techniques with each other. One additional study compared the outcomes of one reconstructive technique at two different types of implants (Roccuzzo, Bonino, Bonino, & Dalmaso, 2011), while another two reported outcomes of treatment at different defect configurations (Roccuzzo, Gaudio, Lungo, & Dalmaso, 2016; Schwarz et al., 2010). Schwarz et al. (2012) assessed two methods of surface decontamination prior to one reconstructive approach. The remaining five studies did not include any comparative analyses (Behneke, Behneke, & d'Hoedt, 2000; Matarasso, Iorio Siciliano, Aglietta, Andreuccetti, & Salvi, 2014; Nart, de Tapia, Pujol, Pascual, & Valles, 2017; Roos-Jansåker, Renvert, Lindahl, & Renvert, 2007a; Wiltfang et al., 2012).

3.2.2 | Study samples

Sample sizes varied from 29 to 63 patients for the controlled studies and from 11 to 75 patients for the studies lacking controls. Roughly, every second study included selected participants, while

the remaining studies described consecutive patient enrolment. In 10 studies, patients with medical conditions (e.g., uncontrolled diabetes) were excluded. Heavy smoking was an exclusion criterion in 5 studies.

All studies were based exclusively on samples from European populations. Four studies reported on patients treated in a private practice setting, while the others reported on patients treated in a specialist or university setting. One study (Jepsen et al., 2016) included multiple centres, while the remaining investigations were performed at single clinical centres. A formal power calculation was described in six (Aghazadeh et al., 2012; Ished et al., 2016; Jepsen et al., 2016; Schwarz et al., 2010, 2012; Wohlfahrt et al., 2012) of the 16 included studies.

Mean age of included patients ranged from 48 to 71 years, and the ratio between males and females included varied from 0.9 to 0.1. The proportion of smokers ranged from 15% to 70%. In 5 studies, only one single type of implant was included, while 2 to 11 different implant brands were treated in the remaining studies. Prerequisites for the peri-implant defects to be treated varied considerably between studies. Eight studies, for instance, did not specify the presence of signs of inflammation (e.g., BOP) for inclusion. All studies but two (Roos-Jansåker et al., 2007a,b), however, required the presence of an angular bone defect. Requirements in terms of depth of the bone defect ranged from a minimum of 3 to 4 mm. Two studies (Jepsen et al., 2016; Nart et al., 2017) further specified the peri-implant defects in terms of configuration (for details, see Table A-2).

3.2.3 | Interventions

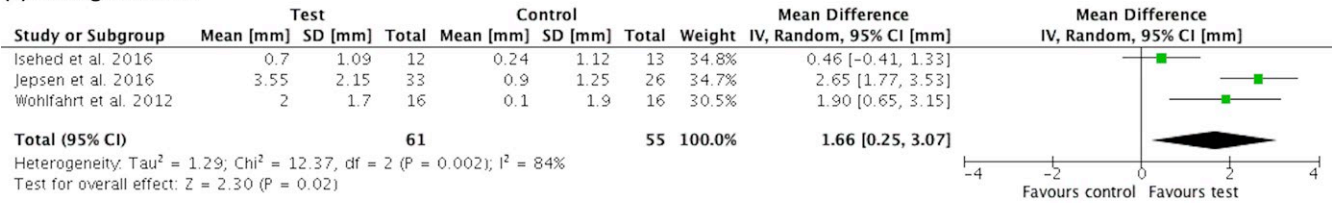
In two of the three controlled studies, porous titanium granules were used in the intervention groups (Jepsen et al., 2016; Wohlfahrt et al., 2012), while the third evaluated the potential benefit of enamel matrix derivate (Ished et al., 2016).

All of the studies without controls used bone replacement grafts, either alone (Behneke et al., 2000; Khoury & Buchmann, 2001; Roccuzzo et al., 2011, 2016; Roos-Jansåker et al., 2007b; Schwarz et al., 2008; Wiltfang et al., 2012) or in combination with membranes (Aghazadeh et al., 2012; Khoury & Buchmann, 2001; Matarasso et al., 2014; Nart et al., 2017; Roos-Jansåker et al., 2007a,b; Schwarz et al., 2008, 2010, 2012). The most commonly used graft material was bovine bone mineral as particles (Aghazadeh et al., 2012; Matarasso et al., 2014; Schwarz et al., 2008, 2010, 2012) or as a block (Roccuzzo et al., 2011, 2016). Hydroxyapatite and autologous bone grafts were applied in 3 (Roos-Jansåker et al., 2007a,b; Schwarz et al., 2008) and four (Aghazadeh et al., 2012; Behneke et al., 2000; Khoury & Buchmann, 2001; Wiltfang et al., 2012) studies, respectively. One study described the use of an allograft (Nart et al., 2017).

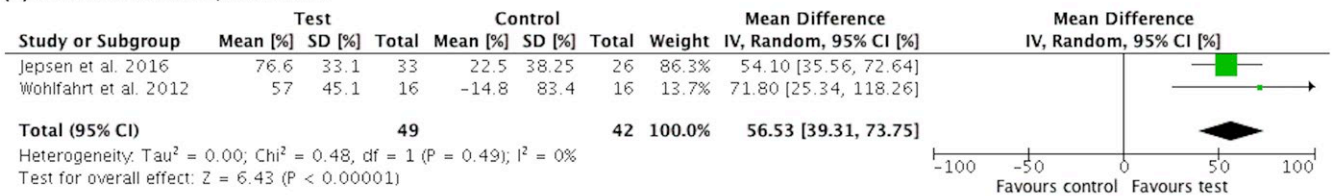
3.3 | Risk of bias in individual studies

The assessment of risk of bias in the included randomized trials is illustrated in Table A-3. A low risk of bias was noted in one study only (Ished et al., 2016), based on the apparent difficulty to blind

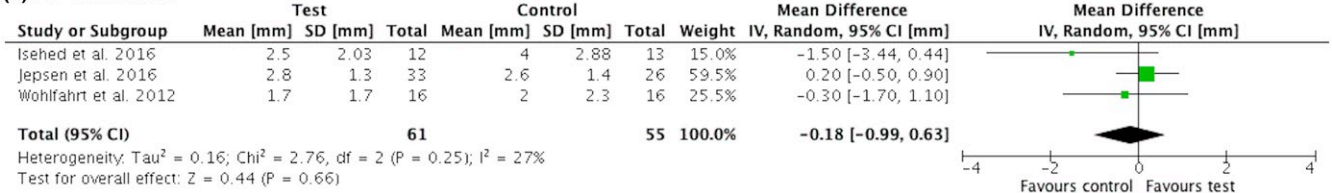
(a) Change of MBL



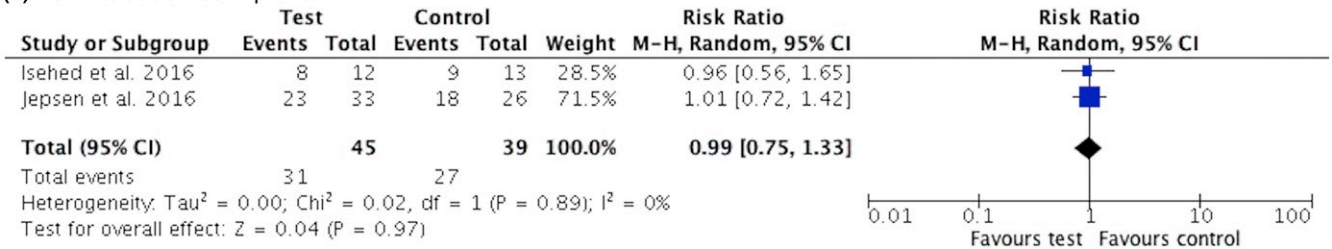
(b) Defect reduction/defect fill



(c) PD reduction



(d) BOP reduction at implants



(e) BOP reduction at implant sites

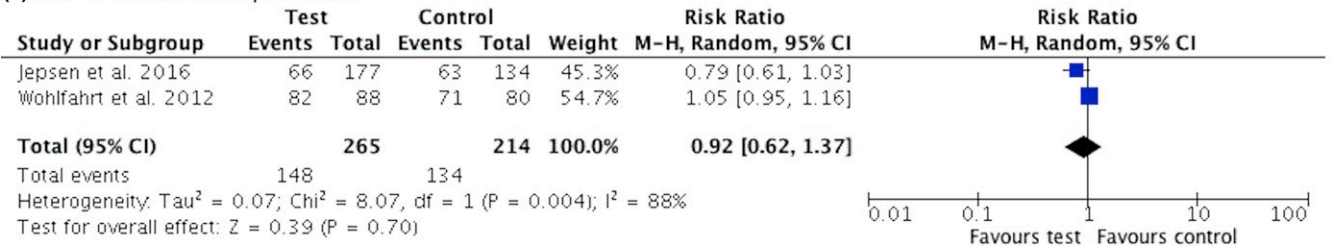


FIGURE 2 (a) Forest plot. Potential benefit in terms of change of MBL (studies with controls). Unit of analysis: implant. Additional data kindly provided by Isehede et al. (2016). For Jepsen et al. (2016): average of mesial and distal. (b) Forest plot. Potential benefit in terms of defect reduction/defect fill [%] (studies with controls). Unit of analysis: implant. For Jepsen et al. (2016): average of mesial and distal. (c) Forest plot. Potential benefit in terms of PD reduction (studies with controls). Unit of analysis: implant. Additional data kindly provided by Isehede et al. (2016). For Jepsen et al. (2016): average of mesial and distal. (d) Forest plot. Potential benefit in terms of BOP reduction at implants (studies with controls). Unit of analysis: implant. Number of events estimated based on reported percentages. (e). Forest plot. Potential benefit in terms of BOP reduction at implant sites (studies with controls). Unit of analysis: implant site. Number of events estimated based on reported percentages or numbers

the examiner during radiological assessments in the studies evaluating bone replacement grafts (detection bias). In addition, a substantial patient dropout was noted for the long-term follow-up (7 years) for two studies (Andersen, Aass, & Wohlfahrt, 2017; Schwarz et al., 2017). This, however, was not relevant for outcomes at 12 months.

The quality of reporting in the selected observational studies is depicted in Table A-4. Three of the studies (Rocuzzo et al., 2016;

Schwarz et al., 2010; Wiltfang et al., 2012) met all of the quality categories.

3.4 | Risk of bias across studies

No significant publication bias was observed for the three controlled studies in terms of change of MBL and PD reduction (Figure A-1a and

b). Considering only reconstructive interventions from controlled and uncontrolled studies, the funnel plots indicated no significant publication bias for change of MBL but indicated a significant bias for PD reduction (Figure A-2a and b).

3.5 | Potential benefit of reconstructive surgical therapy

The analysis included a total of 116 implants for the primary outcome. For the secondary outcomes, the number of included implants varied from 84 to 116. Heterogeneity among studies expressed as I^2 varied from 0% to 88%, depending on the outcome measure.

3.5.1 | Primary outcome: change of radiographic marginal bone level

Figure 2a illustrates the results of the meta-analysis for changes of MBL. All three studies with controls reported on the primary outcome. A statistically significant benefit (WMD = 1.7 mm; 95% CI: 0.3/3.1; $p = 0.02$) was observed in favour of the reconstructive interventions.

3.5.2 | Secondary outcomes

Defect fill was reported in two of the studies with controls (Figure 2b), indicating a statistically significant greater fill at test sites (WMD = 56.5%; 95% CI: 39.3/73.8; $p < 0.001$). The analysis failed to identify a significant benefit in terms of PD reduction, based on data from all three studies (Figure 2c). Similar findings were made for BOP reduction. The RR for BOP reduction was 1.0 (95% CI: 0.8/1.3; $p = 0.97$) and 0.9 (95% CI: 0.6/1.4; $p = 0.70$) for implants and implant sites, respectively (Figures 2d and e). None of the studies with controls reported on changes of CAL, REC or PROMs. Implant survival over at least 5 years was described in one of the interventional studies (Andersen et al., 2017). Over a 7-year follow-up, 3 of 17 implants were lost in three patients, all belonging to the test group (porous titanium granules).

3.6 | Outcome of reconstructive surgical therapy

The analysis included a total of 433 implants for the primary outcome. For the secondary outcomes, the number of included implants varied from 147 to 821. Heterogeneity among studies, namely the percentage of variation due to a true variation between treatment effects in relation to the variation due to sampling error, varied from 51% to 95%.

3.6.1 | Primary outcome: change of radiographic marginal bone level

Figure 3a illustrates the reduction of MBL from baseline to 12 months postsurgery. Based on 11 arms in seven studies, the WMD amounted to 2.0 mm (95% CI: 1.3/2.7; $p < 0.001$). The prediction interval, that

is the expected range of the outcome of treatment applied to a random subject of the overall studied population, was $-0.4/4.4$ mm. Estimates were consistent, regardless of study design.

3.6.2 | Secondary outcomes

A CAL gain of 1.8 mm (95% CI: 1.3/2.2; $p < 0.001$) with a prediction interval of 0.6/3.0 (Figure 3b) was observed based on findings from four studies. Change of REC was assessed in six studies (10 arms) and amounted to -0.7 mm (95% CI: $-1.0/-0.3$; $p < 0.001$) (Figure 3c). The prediction interval was $-1.7/0.4$. PD reduction is illustrated in Figure 3d. The weighted mean effect was 2.8 mm (95% CI: 2.3/3.4; $p < 0.001$) at 12 months, based on 21 arms in 13 studies. The prediction interval was estimated to be 0.4/5.3 mm. Reduction of inflammation at 12 months was statistically significant. The RR for BOP was 0.4 (95% CI: 0.2/0.8; $p = 0.004$) and 0.2 (95% CI: 0.2/0.4; $p < 0.001$) for implants and implant sites, respectively (Figure 3e and f). The respective prediction intervals were 0.1/2.3 and 0.0/1.7. Results of the sensitivity analysis revealed that the RR for BOP for implants was considerably lower in studies with controls (0.07; 95% CI: 0.0/0.5) than without (0.51; 95% CI: 0.3/0.8).

None of the studies without controls reported on defect fill or PROMs, while implant survival over at least 5 years was described in two. Results ranged from 83% (Roccuzzo et al., 2017) to 100% (Roos-Jansåker, Persson, Lindahl, & Renvert, 2014) on the implant level.

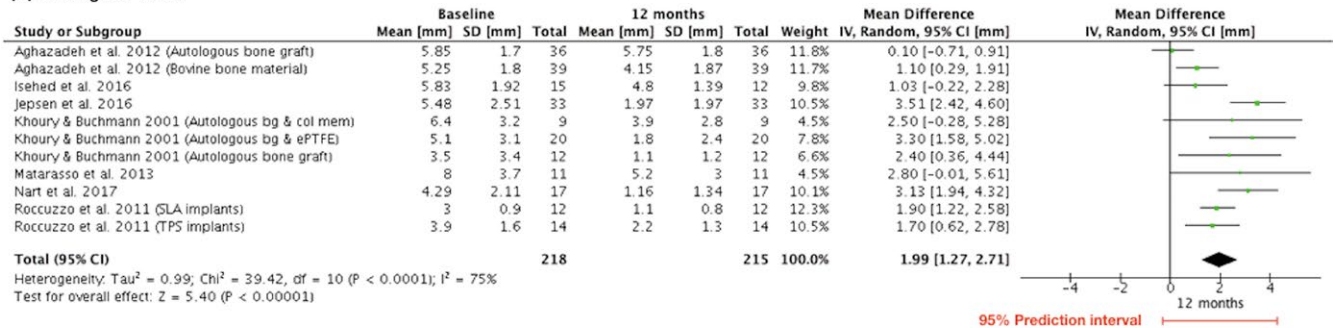
4 | DISCUSSION

The present systematic review aimed at evaluating the efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects. The potential benefit of reconstructive techniques over control procedures was evaluated in three studies, representing a total of 116 implants. Altogether, 16 studies reported on the outcome of reconstructive measures at 12 months after surgery. The meta-analyses identified a statistically significant larger MBL gain (WMD = 1.7 mm) and defect fill (WMD = 57%) for test procedures, but found no differences for clinical measures (PD reduction, BOP reduction). Changes of clinical attachment and soft tissue levels were not considered.

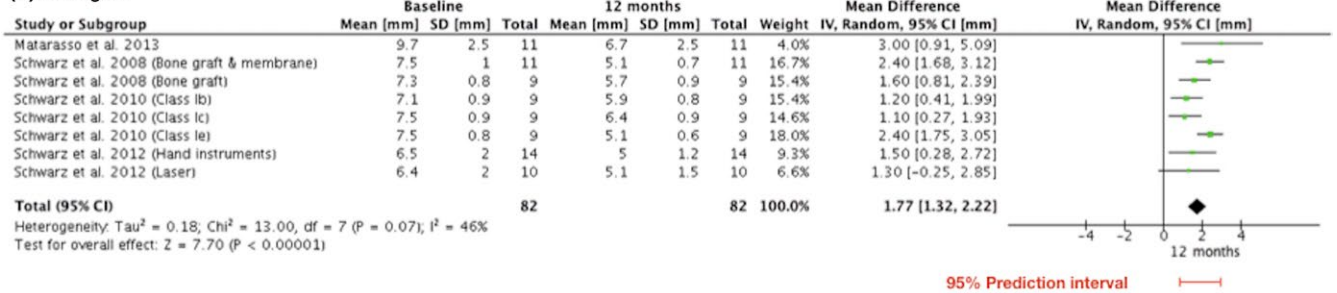
In terms of overall outcome, therapy resulted in improved MBL (WMD = 2.0 mm) and CAL (WMD = 1.8 mm), in recession (WMD = 0.7 mm), in reduced PD (WMD = 2.8 mm) and in reduced BOP (Implants: RR = 0.4/Sites: RR = 0.2). None of the included studies addressed patient-reported outcome measures.

Results of the present meta-analyses are in line with calculations presented in previously published systematic reviews on the topic (Chan, Lin, Suárez, MacEachern, & Wang, 2014; Khoshkam et al., 2013, 2016; Sahrman, Attin, & Schmidlin, 2011). The present analysis suggests that reconstructive therapy at peri-implantitis-related defects is a feasible concept, but it is also obvious that the available evidence is limited. The majority of studies identified in the present review was observational and had the characteristics of case series.

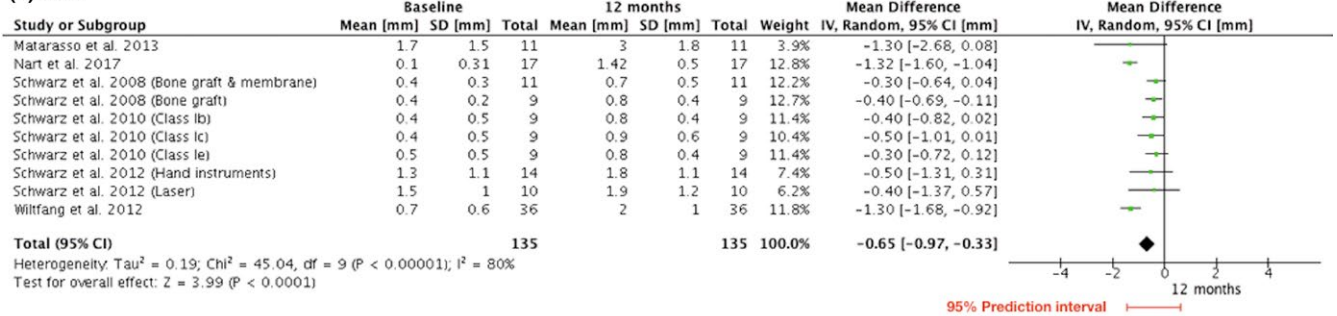
(a) Change of MBL



(b) CAL gain



(c) REC



(d) PD reduction

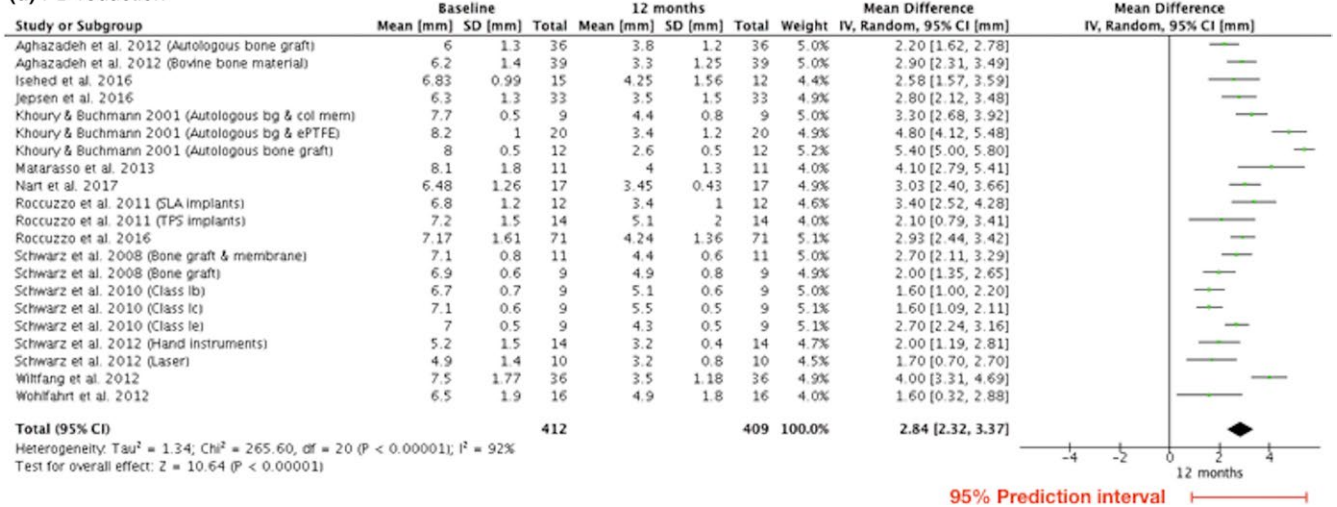


FIGURE 3 (continued)

Only three of the included studies were randomized controlled trials addressing the scientific question of the present review, that is the potential benefit of reconstructive measures over open-flap debridement alone. None of the included study samples originated from outside of

Europe, which represents a limitation in terms of generalizability. In addition, most studies were conducted at specialist or university clinics. The significant heterogeneity within and between samples may in part be attributed to the different techniques and materials used and

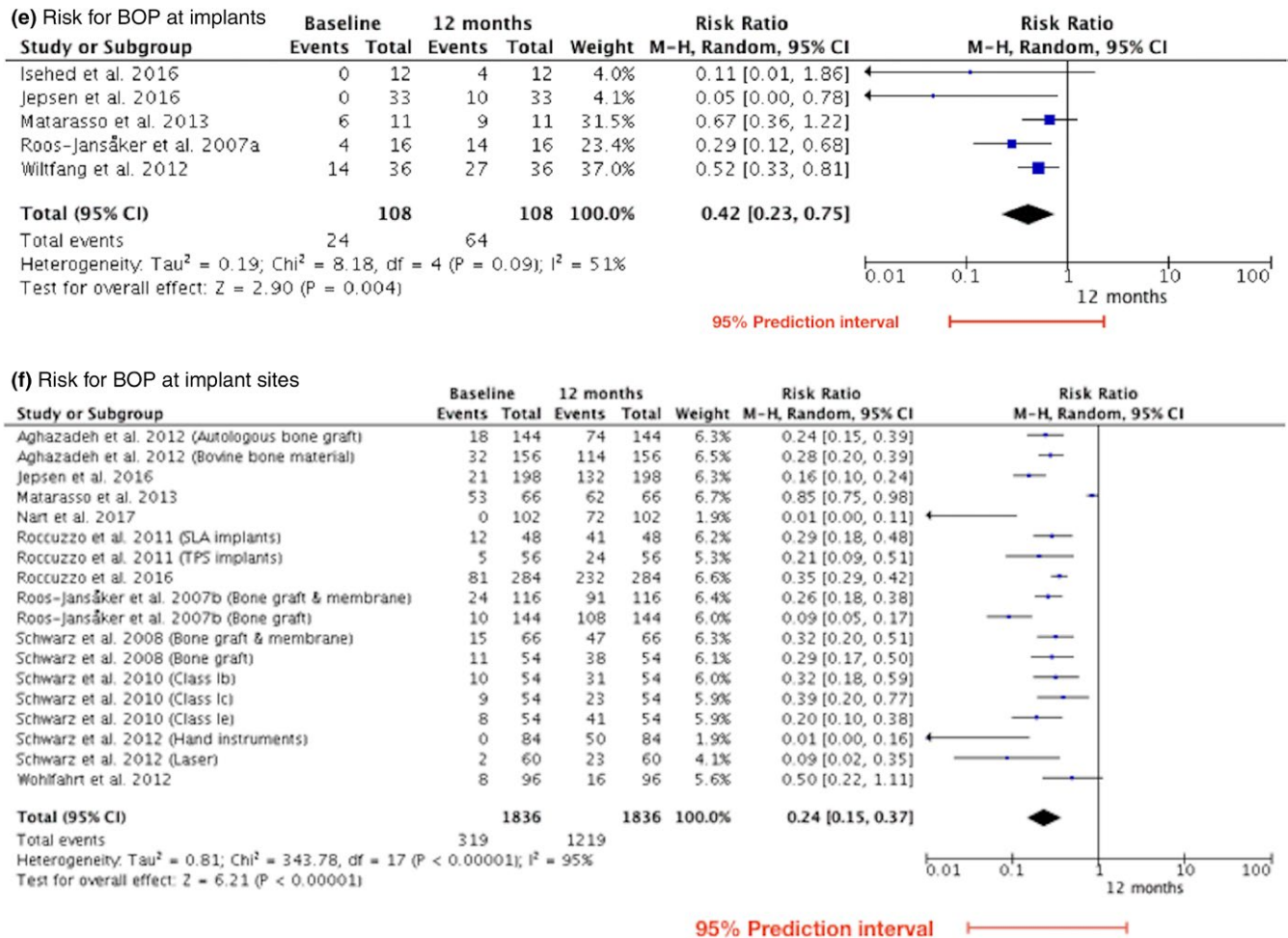


FIGURE 3 (a) Forest plot. Reduction of MBL (reconstructive interventions from controlled and uncontrolled studies). Unit of analysis: implant. Additional data kindly provided by Isehede et al. (2016). Not considered: Baseline and/or 12-month bone levels (mean) not reported: Roccuzzo et al. (2016), Roos-Jansåker et al. (2007a,b), Schwarz et al. (2008, 2010, 2012), Wiltfang et al. (2012), Wohlfahrt et al. (2012). SE or SD of mean values not reported: Behneke et al. (2000). (b) Forest plot. CAL gain (reconstructive interventions from controlled and uncontrolled studies). Unit of analysis: implant. Not considered: Baseline and/or 12-month clinical attachment levels (mean) not reported: Aghazadeh et al. (2012), Isehede et al. (2016), Jepsen et al. (2016), Khoury and Buchmann (2001), Nart et al. (2017), Roccuzzo et al. (2011, 2016), Roos-Jansåker et al. (2007a,b), Wiltfang et al. (2012), Wohlfahrt et al. (2012). SE or SD of mean values not reported: Behneke et al. (2000). (c) Forest plot. Change of soft tissue level (REC) (reconstructive interventions from controlled and uncontrolled studies). Unit of analysis: implant. Not considered: Soft tissue levels (mean) at baseline and/or 12 months not reported: Aghazadeh et al. (2012), Behneke et al. (2000), Isehede et al. (2016), Jepsen et al. (2016), Khoury and Buchmann (2001), Roccuzzo et al. (2011, 2016), Roos-Jansåker et al. (2007a,b), Wohlfahrt et al. (2012). (d) Forest plot. PD reduction (reconstructive interventions from controlled and uncontrolled studies). Unit of analysis: implant. Additional data kindly provided by Isehede et al. (2016). Not considered: Baseline and/or 12-month PD (mean) not reported: Roos-Jansåker et al. (2007a,b). SE or SD of mean values not reported: Behneke et al. (2000). (e) Forest plot. Risk for BOP at implants (reconstructive interventions from controlled and uncontrolled studies). Unit of analysis: implant. Not considered: BOP% (implants) at baseline and/or 12 months not reported: Aghazadeh et al. (2012), Behneke et al. (2000), Khoury and Buchmann (2001), Nart et al. (2017), Roccuzzo et al. (2011, 2016), Roos-Jansåker et al. (2007b), Schwarz et al. (2008, 2010, 2012), Wohlfahrt et al. (2012). (f) Forest plot. Risk for BOP at implant sites (reconstructive interventions from controlled and uncontrolled studies). Unit of analysis: implant site. Not considered: BOP% (sites) at baseline and/or 12 months not reported: Behneke et al. (2000), Isehede et al. (2016), Khoury and Buchmann (2001), Roos-Jansåker et al. (2007a), Wiltfang et al. (2012)

to inconsistent inclusion/exclusion criteria. The gender ratio among selected study populations varied considerably, as did the proportion of smokers and patients with systemic conditions. There was also a noteworthy discrepancy in terms of selection of grafting material among the included articles. The most commonly used material in the uncontrolled, observational studies was bovine bone mineral, while none of the controlled studies evaluated this specific product.

The variation of outcomes between study samples was explored by I^2 , illustrating the proportion of variance exceeding the sampling error (true variance) (Higgins & Thompson, 2002; Higgins et al., 2003). The prediction intervals observed in the present meta-analyses showed a wide range of expected effects, also indicating a significant variability between the included studies (Borenstein et al., 2017; Int'Hout, Ioannidis, Rovers, & Goeman, 2016). For

example, in terms of MBL changes, the expected outcome ranged from no effect at all (0 is included) or bone loss to improvement of marginal bone level of 4.4 mm. It should be kept in mind that the 95% CI of the estimate simply reflects the precision of the estimation of the mean value. The prediction interval, however, is an index of dispersion, indicating how widely the effect varies across a given population (Borenstein et al., 2017).

In the consensus report from the 8th European Workshop on Periodontology, it was suggested to use composite outcomes to describe results of peri-implantitis therapy (Sanz & Chapple, 2012). These should ideally include clinical measures of inflammation and radiographic assessments of bone-level alterations. Following these recommendations, studies applying pocket elimination techniques (Carcuac et al., 2016, 2017) or reconstructive techniques (Aghazadeh et al., 2012; Jepsen et al., 2016) have reported results accordingly. An additional goal of reconstructive therapy is the maintenance of soft tissue height. None of the controlled studies, however, reported data on soft tissue alterations. The recession observed in observational studies (WMD = 0.7 mm) was statistically significant and corresponded well with findings reported in studies on periodontal reconstructive therapy (Heden, Wennström, & Lindhe, 1999; S. Jepsen et al., 2008; Tonetti et al., 2004, 2002; Trombelli, Simonelli, Minenna, Rasperini, & Farina, 2017). It remains unclear, however, whether the reconstructive techniques applied at peri-implant defects resulted in a better aesthetic outcome as compared to controls.

Studies with controls indicated a benefit of 1.7 mm in favour of reconstructive measures for changes of marginal bone level. It should be kept in mind, however, that two of the three controlled studies (Jepsen et al., 2016; Wohlfahrt et al., 2012) used porous titanium granules as bone replacement graft in the test groups. It is obvious that blinding of the examiner during radiographic assessments in such studies was not possible. Further, it is unclear how the presence of a radiopaque grafting material affected the assessment of marginal bone levels as neither study reported measurement errors. Ished et al. (2016), who used enamel matrix derivative in the test group, reported a moderate benefit of 0.5 mm. Considering all different reconstructive interventions included in the present review, marginal bone levels were improved by 2.0 mm on average. However, the prediction interval was wide and included 0, indicating a high degree of variability.

Despite the observed potential benefit in radiographic appearance, reconstructive therapy did not provide any benefit in terms of reduction of PD and BOP. Considering overall changes from baseline to 12 months, however, peri-implant inflammation was significantly reduced by the surgical treatment. The analysis showed that it was more likely to arrest bleeding at a single site (RR = 0.2) than to achieve peri-implant health at all aspects of the affected implant (RR = 0.4). Data reported by Jepsen et al. (2016) further illustrate this observation. While the percentage of bleeding sites was reduced by 45% and 56% in control and test groups, respectively, the proportion of

implants free of any bleeding at 12 months was 30% for both groups. Similar figures have been described in studies applying pocket elimination techniques. Thus, Carcuac et al. (2017) and Heitz-Mayfield et al. (2018) reported 40% of implants to be completely free of bleeding at 3 and 5 years, respectively. Again, a high variation in terms of expected change of BOP at site and implant levels was testified, as illustrated by wide prediction intervals.

The present work suffers from a number of shortcomings. Data from pre-clinical (e.g., Albouy et al., 2011; Carcuac et al., 2015) and clinical studies (e.g., Berglundh et al., 2018; Rocuzzo et al., 2017) on surgical therapy of peri-implantitis pointed towards the impact of implant surface characteristics on treatment outcomes. Further, inclusion criteria in regard to the configuration of peri-implant defects differed between studies, which may have influenced subsequent healing (Schwarz et al., 2010). And finally, the frequency and quality of maintenance therapy following reconstructive procedures may also have been of importance as has been demonstrated for periodontitis patients (Cortellini, Pini Prato, & Tonetti, 1994). Neither of these factors was, however, considered in the present meta-analyses. In the secondary calculation of the overall changes, measures from baseline and 12 months were handled as independent data sets. It may be argued that treatment outcomes are, in fact, correlated to the initial situation. In addition, different treatment arms originating from the same study were considered to be independent of each other. This may have affected assessment of heterogeneity.

In conclusion, the available evidence on reconstructive therapy at peri-implantitis-related defects is limited by (a) the low number of controlled studies, (b) the lack of controlled studies for commonly used procedures, (c) the heterogeneity between studies and (d) the choice of outcome measures. A high variability for predicted outcomes at 12 months was noted. The interpretation of the demonstrated larger MBL gain for test procedures is difficult as graft material may not be distinguishable from newly formed bone. Potential aesthetic and patient-reported advantages remain to be demonstrated.

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CONFLICT OF INTEREST

The authors declare no conflict of interest with respect to the authorship and/or publication of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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