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Review

Long-Term Prognosis of Peri-Implantitis Treatment: A Systematic Review of Prospective Trials with More Than 3 Years of Follow-Up

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Featured Application: Regenerative approaches for treatment of peri-implantitis lead to favorable long-term clinical outcomes and survival rate.

Abstract: A multitude of clinical trials have tested therapeutic approaches to treat peri-implantitis but there is still no consensus on what treatment modality leads to the most favorable clinical improvement and reduced implant loss. Therefore, the present systematic review reported on the long-term clinical and radiological outcomes after treatment of peri-implantitis with different surgical approaches. A PICO question was defined; manual and electronic searches were completed to screen for human prospective studies with at least 3 years of follow-up after surgical treatment of peri-implantitis. Analyses were performed using a random-effect model. Thirteen trials reported on 706 implants and 399 patients. Open flap, resective and reconstructive approaches led to a probing depth reduction of 2.23, 2.25 and 3.78 mm with a survival rate of 84%, 90% and 95%, respectively. Reconstructive treatments were followed by an average of 2.34 mm of radiographic bone gain, flap had negligible bone changes (0.11 mm) and resective approaches resulted in a mean bone loss of 0.5 mm. Large heterogeneity existed among studies for diagnostic criteria and decontamination modalities. Within the existing limitations, regenerative approaches for the treatment of peri-implantitis lead to advantageous long-term improvement of peri-implant tissues and higher implant survival rate.

Keywords: dental implants; peri-implantitis; therapeutics; systematic review

1. Introduction

Peri-implantitis is a destructive inflammatory disease of soft and hard tissues surrounding dental implants [1]. Due to the large prevalence [2,3], accelerating pattern of progression [4], and unknown predisposing factors [5], peri-implantitis represents one of the unsolved challenges of the contemporary implant dentistry. Current evidence has shown non-surgical treatment of peri-implantitis to be ineffective with disease control in only 22% of treated cases [6,7], while surgical therapies are followed by more favorable treatment prognosis [8]. A 7 year study on reconstructive treatment of peri-implantitis reported 83% of implant survival rate [9] and a 2–11 year retrospective study showed 78% of implants with no further bone loss after resective treatment [10]. Over the years, different types of surgical interventions have been proposed, and no clear evidence exists to define a single most predictable approach [11]. Proposed treatments are complex combinations of mechanical devices, chemical agents,

and grafting materials, with or without the adjunctive use of antibiotics [12]. The interest in the treatment of peri-implantitis led several authors to publish long-term results of their previous clinical trials [9,13,14]. Literature on long-term outcomes increased quickly during the last several years and offers the opportunity for systematic reviews to gather conclusions based on a larger sample size. In a recent systematic review, Roccuzzo et al. reported that the implant survival rate dropped from 99% to 91% from 3 to 5 years [15]. The patient-based implant survival rate decreased from 99% to 86% after the third year. However, biological endpoints such as bone levels and probing depth remain scarce. Hence, a quantitative analysis of long-term studies combining survival rate with biological endpoints and treatment modality would be beneficial and would help to provide recommendations to clinicians. Therefore, the aim of the present systematic review was to investigate longitudinal studies with at least 3 years of follow-up to report on survival rate, clinical and radiographic endpoints after treatment of peri-implantitis.

2. Materials and Methods

The present systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with code CRD42018106888.

2.1. Search Strategy

An electronic search on MEDLINE/PubMed was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [16]: ((dental implants) OR (dental implantation) OR (dental prosthesis implant supported) OR (oral implants) OR (endosseous implants) OR (implant restoration) OR (osseointegrated implants)) AND ((peri-implantitis) OR (periimplantitis) OR (peri-implant disease) OR (periimplant disease) OR (peri-implant complication) OR (periimplant complication) OR (peri-implant infection) OR (periimplant infection)) AND ((treatment) OR (therapy) OR (therapeutics) OR (surgery) OR (surgical) OR (regeneration) OR (regenerative) OR (reconstructive) OR (guided bone regeneration) OR (GBR) OR (bone graft) OR (bone substitute)) AND (long term) AND ((clinical outcomes) OR (implant failure) OR (implant survival) OR (implant success) OR (bone loss) OR (marginal bone loss) OR (bone level changes) OR (marginal bone level) OR (marginal bone resorption) OR (marginal bone remodelling) OR (crestal bone level) OR (crestal bone loss) OR (crestal bone resorption) OR (crestal bone remodeling)).

An additional search from January 2000 was performed from the websites of the most relevant journals of periodontology and oral surgery for retrieval of missing articles. The searches were updated up to March 2020.

2.2. PICO Question

In a pool of patients/implants in need of peri-implantitis treatment, do reconstructive or resective protocols improve clinical outcome if compared to open-flap control groups?

Participants: Dental implants in need of treatment of peri-implantitis according to the definition of the 2017 World Workshop [1] or comparable definitions [17–21].

Intervention: Open-flap surgical interventions, with or without osseous resection, with or without hard tissue grafting, with or without adjunctive use of disinfective protocols.

Comparison: Control group with placebo treatment, or without treatment.

Outcome: Implant survival, clinical and radiographic outcomes after a follow-up of more than 3 years.

2.3. Inclusion Criteria

Prospective human clinical trials evaluating clinical and radiological outcomes after surgical treatment of peri-implantitis were included. No limitations about date of publication, type of treatment (reconstructive, flap for access or resective), use or no use of antibiotics before or after treatment,

roughness of implant surfaces, type of prostheses (cemented or screw retained) and type of implant (bone level or tissue level) were applied.

2.4. Exclusion Criteria

In-vitro studies, animal studies, repeated reports with the same patients, clinical trials with less than 36 months of follow-up or starting with less than 10 implants were excluded. Articles not provided in English were also excluded.

2.5. Statistical Analysis

Studies were clustered into three groups based on the surgical approach used to treat peri-implantitis: (i) flap access, (ii) resective and (iii) reconstructive. Subgroups were plotted separately and contributed independently to the analysis if they reported using different disinfective agents. Probing depth (PD) reduction, recession (REC) increase, radiographic bone gain (RBG) and implant survival at last follow-up were considered the primary outcomes of the study. Data extraction relative to number of patients, number of implants, implant type, diagnostic criteria, pre-surgical protocol, surgical treatment modality, need of re-treatment, clinical outcomes, and follow-up length were extracted by two independent operators (RDG and BS) and compared. A third independent operator (HLW) was contacted in the case of disagreement. Study characteristics, quality and heterogeneity were assessed by the Cochrane Collaboration tool by two independent operators (RDG and BS). Statistical analysis was performed as weighted mean of studies using comparable treatment modality. Statistical analysis was conducted by a primary statistician (MVR) and validated by an independent statistician (ZC). The random-effect model was applied when performing the averages to account for methodological differences among studies. The data on means for each study were pooled using the mean value and standard error (SE) and were weighted by the inverse variance method. SEs were calculated with this measure SE = upper limit of 95% CI—mean/1.96. The number of implants and patients at the study inception, and those that became lost to follow-up, failed or experienced recurrence, were tallied to calculate survival and success. Forest plots were produced to graphically represent size effect and 95% CI of the outcomes. The heterogeneity of results across studies was evaluated using the I^2 statistic, which was interpreted accordingly: 0% to ≥25 (modest), 25% to 50% (moderate), 50% to 75% (substantial) and 75% to 100% (considerable). Differences were considered statistically significant for $p < 0.05$.

3. Results

3.1. Selection Process

The electronic and journal-based searches were conducted in accordance with the PRISMA principles [16] and yielded 314 and 15 additional reports, respectively, for a total of 329 records. During abstract evaluation, 283 references were excluded, and 46 articles were investigated in their full-text form. Furthermore, 27 articles were removed during the full-text investigation, while 19 articles from 13 prospective human clinical trials were included. Four trials [22–25] reported data from the same pool of patients in more than one publication and data were evaluated in order to keep from counting the same population twice. The analysis was therefore finalized on 13 prospective clinical trials (Figure 1). Risk of bias of included studies was assessed according to the Cochrane Collaboration tool and reported in Table 1.

Table 1. Quality assessment of the included studies according to the Cochrane risk of bias tool. Characteristic, quality, and heterogeneity of enrolled studies were reported.

	Risk of Bias						Risk of Bias (Other Sources)				
Study Reference **Low** **High** **N/A**	**Random Sequence Generation**	**Allocation Concealment**	**Blinding of Patients and Operators**	**Blinding of Outcome Assessment**	**Incomplete Outcome Data**	**Selective Reporting**	**Group Imbalance**	**Sample Size**	**Conflict of Interest**	**Radiographic Outcome**	**Biological Assessment**
Mercado et al. 2018	N/A	N/A	N/A	N/A	low	N/A	N/A	high	low	low	low
Isehed et al. 2018	low	low	high	low	high	low	low	low	high	low	low
Heitz-Mayfield et al. 2018	N/A	N/A	N/A	N/A	low	N/A	N/A	low	low	high	low
Roccuzzo et al. 2017	N/A	N/A	N/A	N/A	low	N/A	N/A	high	low	low	low
Carcuac et al. 2017	low	low	high	low	low	low	low	low	low	low	low
Froum et al. 2015	N/A	N/A	N/A	N/A	low	N/A	N/A	N/A	low	low	high
Serino et al. 2015	N/A	N/A	N/A	N/A	low	N/A	N/A	high	low	high	high
Roos-Jansaker et al. 2014	high	high	high	low	low	low	high	high	low	low	low
Schwarz et al. 2009	low	low	high	low	low	low	low	high	high	high	low
Deppe et al. 2007	N/A	N/A	N/A	N/A	high	N/A	N/A	high	low	low	low
Romeo et al. 2005;2007	low	low	high	high	low	low	high	high	low	low	low
Leonhardt et al. 2003	N/A	N/A	N/A	N/A	low	N/A	N/A	high	high	high	high
Khoury and Buchmann 2001	high	high	high	high	low	low	high	high	high	low	low

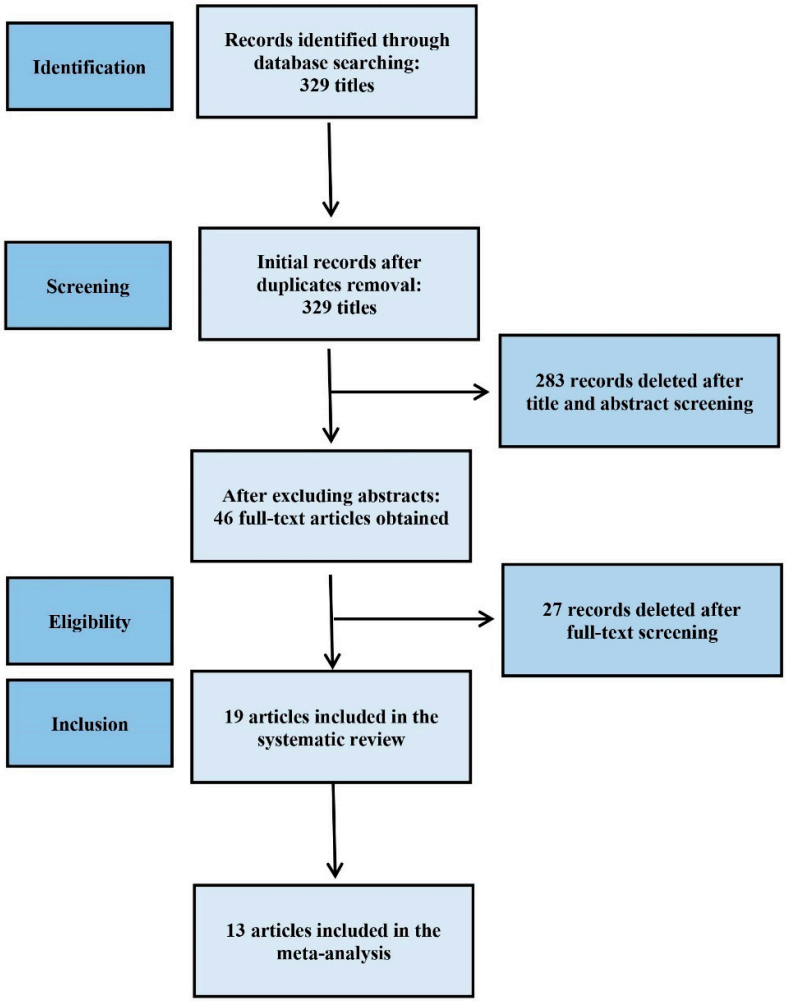


Figure 1. Flow chart for the article selection according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

3.2. Population Pool

Thirteen trials for a total of 21 groups of treatment reported data on 706 implants and 399 patients with a follow-up from 3 to 7 years after surgical intervention for peri-implantitis (Table 2). The most commonly used clinical parameters to diagnose peri-implantitis were:

- Bone loss (BL), reported in % to the length of the implant [26,27], millimeters [14,28–33], number of threads exposed [34], defect morphology [9,14,27,32], or evidence of progressive bone loss [35–37];
- Pathologic probing depth (PD), with a cutoff between health and disease that ranged between >4 mm [27] and >6 mm [9];
- Marginal tissue inflammation reported as bleeding on probing (BoP) or suppuration on probing (SoP) [14,27–31,33–37].
- The sample size of individual studies ranged between 19 implants [14,34] and 168 implants [29]. Studies included a combination of minimally rough and moderately rough implant surfaces, as well as tissue level and bone level macro-designs. Biological criteria to evaluate success after treatment were missing in many trials [26,29,32,35–37]. When reported, cut-off probing depth to consider the treatment successful was set as 4 mm [33] or at 5 mm [9,27,28,30,31]. Radiographic criteria for biological success were defined in seven studies [9,14,27,30,31,33,34] and varied from no further bone loss to 25% of defect fill [31]. Absence of BoP and SoP was required by five studies [9,27,28,30,31]. The mean follow-up in years ranged from 3 years [26–28,36,37] to 7 years [9].

Table 2. Demographics and diagnostic criteria of included articles. Abbreviations, BoP: bleeding on probing (+/−). BL: bone loss (mm). N/P: not provided. PD: probing depth (mm). REC: recession (mm). SLA: sandblasted acid-etched. SoP: suppuration on probing (+/−). TPS: titanium plasma-sprayed.

Study Reference	Initial Patient	Initial Implant	Final Patient	Final Implant	Implant Type	Diagnosis	Biological Success	Follow-Up
Mercado et al. 2018	30	30	30	30	N/P	PD > 4 mm BoP/SoP+ BL > 20% Crater defect Function for >2 years	PD < 5 mm BoP/SoP− Further BL < 10% REC < 0.5 mm for anterior implants REC < 1.5 mm for posterior implants	3 y
Isehed et al. 2018	29	15 test 14 contr.	11 test 9 contr.	11 test 9 contr.	Nobel Biocare Astra Tech Straumann Biomet 3	PD ≥ 5 mm BoP/SoP+ Angular BL ≥ 3 mm	No further BL	5 y
Heitz-Mayfield et al. 2018	24	36	20	26	N/P	BL ≥ 2 mm PD ≥ 5 mm BoP/SoP+	PD < 5 mm BoP/SoP− No further BL	5 y
Roccuzzo et al. 2017	26	12 SLA 14 TPS	12 SLA 12 TPS	12 SLA 12 TPS	Strauman	PD > 6 mm Crater defects	PD ≤ 5 mm BoP/SoP− No further BL	7 y
Carcuac et al. 2017	100	179	83	148	Nobel Biocare Astra Tech Straumann Neoss	PD ≥ 6 mm BoP/SoP+ BL ≥ 3 mm	PD ≤ 5 mm BoP/SoP− Further BL ≤ 0.5 mm	3 y
Froum et al. 2015	100	170	98	168	Biomet 3i Nobel Biocare IMZ Zimmer BioHorizons Frialit Straumann Astra Tech Bicon Innova	PD ≥ 5 mm BL ≥ 3 mm BoP+	N/P	3.6 y

Table 2. *Cont.*

Study Reference	Initial Patient	Initial Implant	Final Patient	Final Implant	Implant Type	Diagnosis	Biological Success	Follow-Up
Serino et al. 2015	31	N/P	27	71	Branemark Astra Tech Straumann	PD ≥ 6 mm BoP/SoP+ BL ≥ 2 mm Function for > 1 year	PPD < 4 mm No further BL	5 y
Roos-Jansaker et al. 2014	38	29 test 36 contr.	25	23 test 22 contr.	Astra Tech Nobel Biocare	BL > 1.8 mm BoP/SoP+	PD ≤ 5 mm BoP ≤ 1 Bone gain ≥ 25% defect	5 y
Schwarz et al. 2009	22	22	19	19	N/P	PD > 6 mm Intrabony BL > 3 mm	N/P	4 y
Deppe et al. 2007	32	73	N/P	57	IMZ Frialit Nobel Biocare Straumann	Progressive BL PD ≥ 5 mm BoP+	N/P	5 y
Romeo et al. 2005, 2007	19	20 test 18 contr.	19	20 test 18 contr.	Straumann	BoP/SoP+ PD > 4 mm Progressive BL	N/P	3 y
Leonhardt et al. 2003	9	26	9	19	Nobrel Biocare	BL ≥ 3 threads BoP/SoP+ Function for >2 years	No further BL	5 y
Khoury and Buchmann 2001	25	41	25	41	IMZ	BL > 50%	N/P	3 y

3.3. Intervention and Comparison

All authors except one [34] reported that investigated patients underwent one or more sessions of scaling and root planing or another type of non-surgical intervention before surgical therapy. Serino et al. (2015) additionally mentioned that over-contoured prostheses were modified before the surgical phases of the study. Eight articles investigated one or more disinfective protocols applied for reconstructive treatments [9,14,26,27,29,31,32,35], three for resective treatments [33,35–37] and three for flaps access [30,34,35] (Table 3). Among reconstructive interventions, two authors tested the use of biologics as enamel matrix derivatives (EMD) [14,29] or platelet-derived growth factor (PDGF) [29]. Mercado et al. (2018) used a combination of EMD and bovine bone and all other authors advocated for particulate bone grafting with or without barrier membrane. In regard to implant surface decontamination, mechanical instrumentation was aided by the adjunctive use of chlorhexidine [9,26,29,33], hydrogen peroxide [26,34], etching agents such as ethylenediaminetetraacetic acid (EDTA) or citric acid [9,26,27], local application of antibiotics [27,29,36,37], air abrasive devices [29,35], CO_2 laser [35], implantoplasty [36,37], or mechanical instrumentation only [14,30,32]. Every trial described a postoperative chemical regimen with prescribed antibiotics or chlorhexidine (CHX) except for two articles [29,35] where post-operative care was not mentioned. During the reported follow-up period, patients of seven articles were diagnosed with new disease and were treated with new surgical intervention [9,14,29,32], with non-surgical therapy plus antibiotics [30], or with antibiotics only [34] in the event of worsened clinical conditions.

3.4. Outcome

All treatment modalities were successful in achieving favorable biological outcomes after therapy. Radiographic bone gain (Figure 2) was negligible for flap access procedures (0.11mm; 95% CI, −0.56–0.79; I^2: 96%); bone loss (−0.50 mm; 95% CI, −1.30–0.30; I^2: 17%) was noted after resective interventions, and 2.34 mm of radiographic bone gain (95% CI, 1.64–3.03; I^2: 91%) was noted following reconstructive treatments. PD reduction for all sets of studies averaged to 3.20 mm (95% CI, 2.41–3.99; Figure 3). Group-based PD reduction resulted in 2.23 mm (95% CI, 0.70–3.76; I^2: 99%) for flap access, 2.25 mm (95% CI, 1.39–3.11; I^2: 73%) for resective interventions, and 3.78 mm (95% CI, 2.96–4.59; I^2: 92%) for reconstructive modalities. All treatment modalities were followed by a small increase in mucosal recession that averaged as 0.89 mm (95% CI, 0.58–1.20; Figure 4). Recession was larger for the flap (1.44 mm; 95% CI, 0.52–2.36; I^2: 84%) and resective approaches (1.28 mm; 95% CI, 0.70–1.85; I^2: 0%) and it was least for the reconstructive group (0.62 mm; 95% CI, 0.29–0.94; I^2: 85%). Four authors reported at least one group of intervention with 100% of implant survival at the last follow-up [26,31,36,38] while survival of other reports ranged between 67% [30] and 98.8% [29]. Overall implant survival rates after treatment of peri-implantitis was of 91% (95% CI, 87–95; Figure 5). Survival rate varied according to treatment modality and averaged as 84% (95% CI, 77–91; I^2: 0%) for the flap access, 90% (95% CI, 82–99; I^2: 92%) for the resective group, and 95% (95% CI, 91–99; I^2: 52.9) for the reconstructive modalities.

Table 3. Intervention, clinical and radiological outcome of included articles. Abbreviations, APF: apically positioned flap. BDX: bovine-derived xenograft. CAF: coronally advanced flap. CHX: chlorhexidine. CPS: plastic curets + cotton pellets soaked in sterile saline. CTG: connective tissue graft. DBBMC: deproteinized bovine bone mineral with 10% collagen. EDTA: ethylenediaminetetraacetic acid. EMD: enamel matrix derivative. ERL: erbium-doped yttrium aluminum garnet laser. FDBA: freeze-dried bone allograft. FTF: full thickness flap. NBM: bovine-derived natural bone mineral. NHA: nanocrystalline hydroxyapatite. NBM + CM: natural bone mineral with a collagen membrane. N/P: not provided. PDGF: platelet-derived growth factor. SRP: scaling and root planning. SLA: sandblasted acid-etched. TPS: titanium plasma-sprayed. w/o: with or without.

	Treatment Provided					Outcome Assessed			
Study Reference	**Pre-Treatment**	**Surgical Treatment**	**Post-Treatment**	**Supportive Therapy**	**Retreatment Needed**	**Biological Outcome**	**Radiographic Outcome**	**Biological Success**	**Implant Survival at Last Follow-Up**
Mercado et al. 2018	SRP	**Reconstructive:** FTF, EDTA, DBBMC + EMD + Doxycycline, w/o CTG, CAF.	CHX	3 to 4 months	No	PD reduction: 5.4 mm REC: 0.06 mm	Bone gain: 4.32 mm	56.7%	100%
Isehed et al. 2018	SRP	**Reconstructive:** FTF, Mechanical instrum. EMD (test) or no-EMD (control)	CHX	3 to 6 months	Yes	N/P	Bone gain: 1.4 mm test 1.3 mm contr.	48%	85% EMD 75% non-EMD
Heitz-Mayfield et al. 2018	SRP	**Flap for access:** FTF, Mechanical instrum.	amoxicillin + metronidazole CHX	3 to 6 months	Yes (SRP + Antibiotics)	PD reduction: 2.1 mm REC: 1.8 mm	Significant bone loss occurred. Mean not provided.	53%	67%
Roccuzzo et al. 2017	SRP	**Reconstructive:** FTF, Mechanical instrum. EDTA, CHX, BDX, w/o CTG, CAF.	Augmentin CHX	N/P	Yes	PD reduction: 3.4 mm SLA 3.8 mm TPS	Bone gain: 2.1 mm SLA 2 mm TPS	58.3% SLA 14.3% TPS	83.3% SLA 71.4% TPS
Carcuac et al. 2017	SRP	**Resective:** FTF, Mechanical instrum. CHX, Bone recontouring, APF	Amoxicillin	3 months	No	PD reduction: 2.73 mm	BL gain: −0.04	69%	81%
Froum et al. 2015	SRP	**Reconstructive:** FTF, Mechanical instrum. Air powder, Tetracycline or minocycline, CHX, EMD or PDGF, FDBA, resorb membrane, CAF.	N/P	2 to 3 months	Yes	PD reduction: 5.10 mm, REC: −0.52 mm.	BL gain: 1.77 mm	N/P	98.8%

Table 3. *Cont.*

Treatment Provided						Outcome Assessed			
Study Reference	**Pre-Treatment**	**Surgical Treatment**	**Post-Treatment**	**Supportive Therapy**	**Retreatment Needed**	**Biological Outcome**	**Radiographic Outcome**	**Biological Success**	**Implant Survival at Last Follow-Up**
Serino et al. 2015	Correction of bad-designed prostheses, SRP	**Resective:** FTF, Mechanical instrum, Bone recontouring, CHX, APF	Clindamycin (7 days), CHX (14 days)	3th and 6th month, then every 6 months.	No	N/P	N/P	61%	97%
Roos-Jansaker et al. 2014	SRP	**Reconstructive:** Pros removal, FTF, H_2O_2, Algipore bone graft, w/o resorb membrane, pros reconnected.	Amoxicillin + metronidazole (10 days), CHX (5 weeks)	6th week, then every 3 months	No	PD reduction: 3.0 mm test, 3.3 mm control	Bone gain: 1.3 mm test 1.1 mm contr.	66.7% −51.1%	100%
Schwarz et al. 2009	SRP, CHX	**Reconstructive:** FTF, Mechanical instrum. NHA (test) or NBM + CM (control), CAF.	CHX (2 weeks)	every 2 weeks for 2 months, once a month for 6 months, then every 6 months for 4y	Yes	PD reduction: 1.1 mm NHA 2.5 mm NBM + CM REC: 0.4 mm NHA 0.5 mm NBM + CM	N/P	N/P	91%
Deppe et al. 2007	SRP, CHX	**Reconstructive:** Pros removal, FTF, Mechanical instrum. air-powder abrasive, w/o CO_2 laser, βTCP+autogenous, non-resorb membrane, submerged healing. **Resective:** FTF, Mechanical instrum. air-powder abrasive, w/o CO_2 laser, exposed healing.	N/P	N/P	No	PD reduction: 1.9 mm nonCO_2 + Resective 2.6 mm nonCO_2+ reconstructive 2.3 mm CO_2 laser + resective 3.2 mm CO_2 laser + reconstr. REC: 1.6mm nonCO_2 + Resective −0.4 mm nonCO_2 + reconstructive 1.7 mm CO_2 laser + resective −0.4 mm CO_2 laser + reconstr.	Bone gain: −0.1 mm nonCO_2 + Resective 3 mm nonCO_2 + reconstructive 0.6 mm CO_2 laser + resective 3.6 mm CO_2 laser + reconstr.	N/P	82%
Romeo et al. 2005, 2007	SRP.	**Resective:** FTF, Bone recontouring, metronidazole gel, tetracycline, w/o implantoplasty, APF	CHX (2 weeks) Amoxicillin (8 days before the surgery).	Yes (interval N/P)	No	PD reduction: 2.57 mm test 1.02 mm control REC: 1.46 mm test 1.41 mm control	Bone gain: 0 mm test −1.49 mm control	N/P	100% test at 3rd y 87.5% control at 2nd y
Leonhardt et al. 2003	N/P	**Flap for access:** Pros removal, FTF, mechanical instrum. H_2O_2, pros reconnected.	CHX (2 weeks), Metronidazole or amoxicillin or combination (N/P).	3 to 6 months	Yes (only antibiotics, no new surgery)	N/P	N/P	57.6%	73%

Table 3. *Cont.*

Treatment Provided						Outcome Assessed			
Study Reference	**Pre-Treatment**	**Surgical Treatment**	**Post-Treatment**	**Supportive Therapy**	**Retreatment Needed**	**Biological Outcome**	**Radiographic Outcome**	**Biological Success**	**Implant Survival at Last Follow-Up**
Khoury and Buchmann 2001	SRP + antimicrobials + Amoxicillin (1 week).	**Reconstructive:** FTF, Mechanical instrum, CHX, Citric acid, H_2O_2, Autogenous bone graft, Without (control) or with non-resorbable (test1) or resorbable (test 2) membrane, CAF.	Amoxicillin (1 week), CHX (N/P)	1st and 2nd week, then between 3 and 6 months	No	PD reduction: 5.1 mm (control), 5.4 mm (test1), 2.6 mm (test2),	Bone gain: 3.2 mm (control), 3.4 mm (test1), 2.3 mm (Test2)	N/P	100%

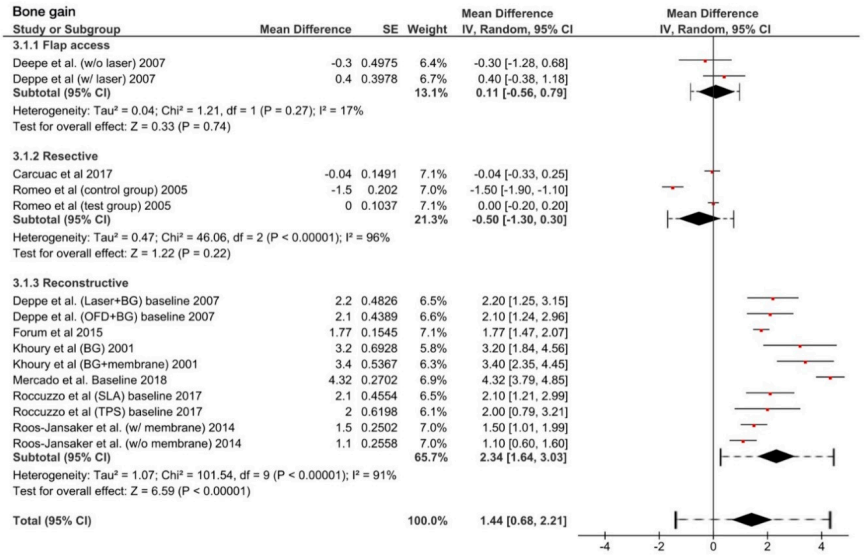


Figure 2. Radiographic bone level changes after treatment of peri-implantitis following flap access, resective or reconstructive approaches. Mean bone gain of each study is reported by a red dot. The 95% confidence interval of each study is indicated with a horizontal line intersecting the mean bone gain. The estimate average and confidence interval of all the individual studies are reported with black diamonds. Prediction intervals are reported as dotted lines intersecting the diamonds. A diamond on the right of the line of null effect indicates bone gain and a diamond on the left of the line of null effect indicates bone loss. Abbreviations. BG: bone grafting, CM: collagen membrane, OFD: open flap debridement, SLA: sandblasted acid-etched surface, TPS: titanium plasma-sprayed surface.

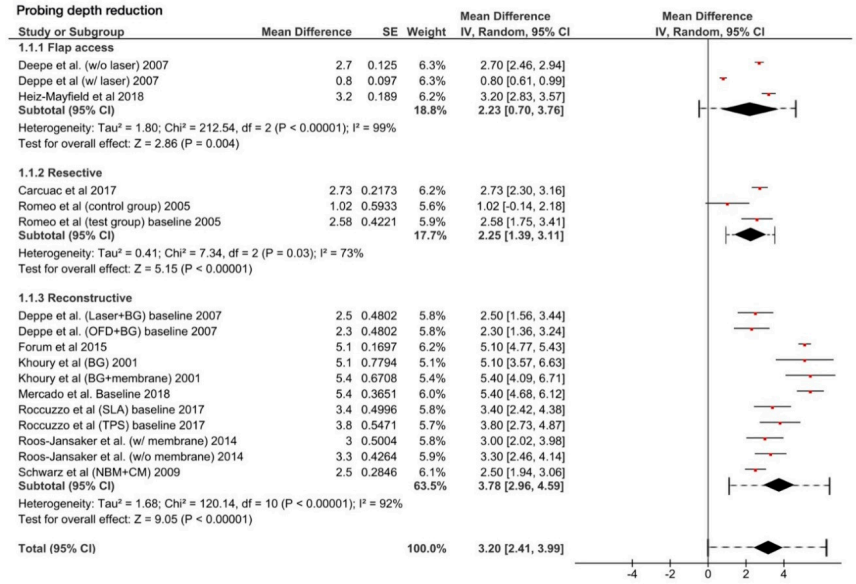


Figure 3. Probing depth reduction after treatment of peri-implantitis following flap access, resective or reconstructive approaches. Mean probing depth reduction in each study is reported by a red dot. The 95% confidence intervals are indicated with horizontal lines intersecting the mean probing depth reduction. The estimate average and confidence interval of all the individual studies are reported with black diamonds. Prediction intervals are reported as dotted lines intersecting the diamonds. A diamond on the right of the line of null effect indicates probing depth reduction and a diamond on the left of the line of null effect indicates probing depth increase. Abbreviations. BG: bone grafting, CM: collagen membrane, OFD: open flap debridement, SLA: sandblasted acid-etched surface, TPS: titanium plasma-sprayed surface.

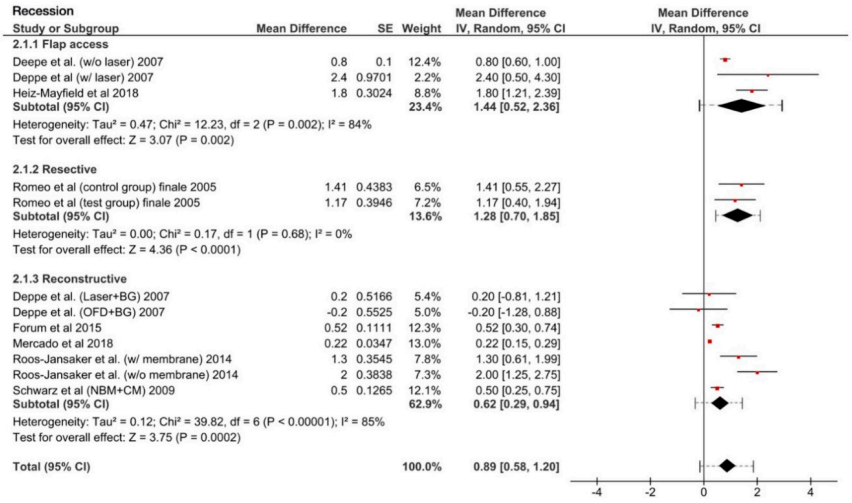


Figure 4. Recession increase after treatment of peri-implantitis following flap access, resective or reconstructive approaches. Mean recession increase in each study is reported by a red dot. The 95% confidence intervals are indicated with horizontal lines intersecting the mean recession. The estimate average and confidence interval of all the individual studies are reported with black diamonds. Prediction intervals are reported as dotted lines intersecting the diamonds. A diamond on the right of the line of null effect indicates recession increase and a diamond on the left of the line of null effect indicates recession reduction. Abbreviations. BG: bone grafting, CM: collagen membrane, OFD: open flap debridement, SLA: sandblasted acid-etched surface, TPS: titanium plasma-sprayed surface.

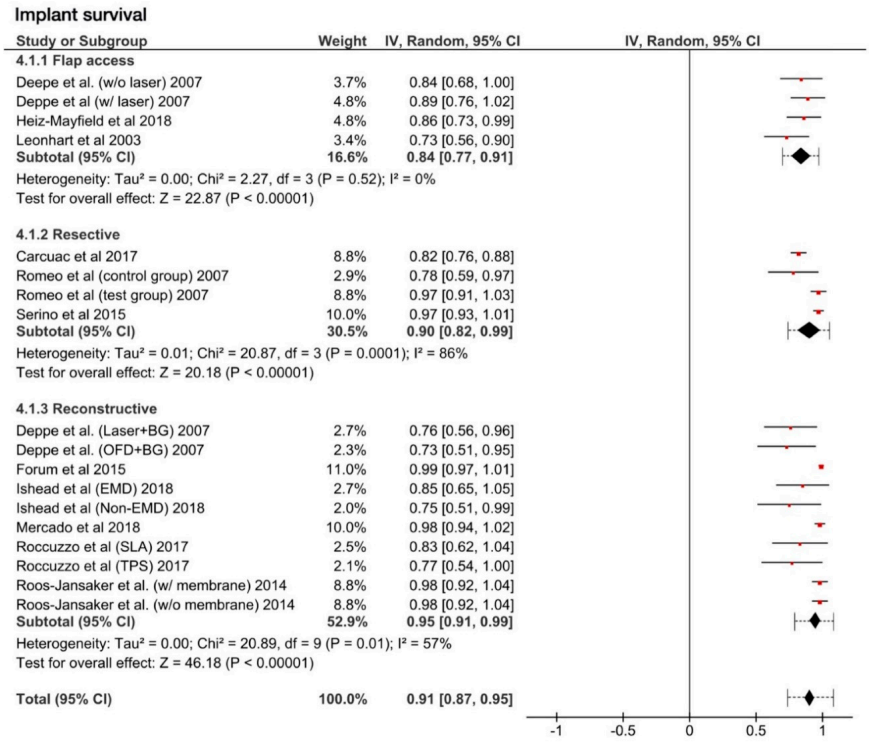


Figure 5. Implant survival rate after treatment of peri-implantitis following flap access, resective or reconstructive approaches. Mean implant survival rate of each study is reported by a red dot. The calculated 95% confidence intervals are indicated with horizontal lines intersecting the mean probing depth reduction. The estimate average and confidence interval of all the individual studies are reported with black diamonds. Prediction intervals are reported as dotted lines intersecting the diamonds. Abbreviations. BG: bone grafting, CM: collagen membrane, EMD: enamel matrix derivatives, OFD: open flap debridement, SLA: sandblasted acid-etched surface, TPS: titanium plasma-sprayed surface.

4. Discussion

The present systematic review integrated data from thirteen human long-term prospective clinical trials and provided weighted averages for clinical and radiographic outcomes after surgical treatment of peri-implantitis. Studies were grouped based on treatment modality and it was found that more favorable bone gain was noted with regenerative approaches, despite successful outcomes for PD reduction and implant survival rate being achieved in all treatment modalities.

Previous systematic reviews on the topic have reported similar findings as the regenerative treatment of peri-implantitis was followed by 2.1 mm of bone fill in Chan et al. [38] and by 2.4 mm in Khoshkam et al. [39], which is very similar to the 2.3 mm of RBG reported in the present systematic review. As most of the peri-implantitis defects have infrabony components [40], regenerative therapies appear advantageous to obtain bone regeneration, and gain peri-implant attachment while minimizing probing depth. Roccuzzo et al. obtained a PD reduction of 3.4 mm and about 2 mm RBG using a regenerative protocol with bovine bone and connective tissue graft [9]. A recent study by Wang et al. used bone allograft and acellular dermal matrix membrane after decontamination with Erbium YAG (Er:YAG) laser and reported 2.25 mm of PD reduction and 1.18 mm of RBG [8]. Froum et al. implemented bovine bone with the use of PDGF or EMD and reported that 91% of the treated implants had 5.1 mm of PD reduction and 1.77 mm of RBG [29].

Regenerative approaches seem advantageous to reconstruct the lost supporting bone in infrabony defects. On the contrary, resective and flap approaches are best indicated for suprabony defects in non-esthetic areas. Berglundh et al. treated 95 implants with open flap debridement together with limited osteoplasty and reported a PD reduction of about 2.5 mm. The estimated probabilities of further bone loss related with residual PD so that the probability of no further bone loss was 83% for postsurgical PD shallower than 5 mm [10]. The same group reported how implants with minimally rough surfaces have 45% more probability to achieve treatment success after resective treatment if compared with moderately rough surfaces [41]. Heitz-Mayfield et al. advocated for open flap debridement without any bone recontouring or implant surface modification. As reported, a saline-soaked gauze was used to rub against the implant surfaces along with copious saline irrigation; in addition, a combination of two adjunctive antimicrobials (amoxicillin and metronidazole) was prescribed as an adjunctive therapy. Mean PD reduction was 2.1 and half of implants had less than 5 mm residual PD, no BoP and no further bone loss [30].

Flap and resective treatment modalities stress the importance of a post-surgical shallow probing depth; however, whether or not residual pockets after therapy represent a risk factor for recurrence of peri-implantitis remains unclear. Serino et al. concluded that residual pathological probing depth is an unfavorable prognostic factor [33]; however, Roos-Jansaker et al. and Heitz-Mayfield et al. reported that a stable peri-implant condition was maintained without correlation with pockets deeper than 5 mm [30,31]. It could be speculated that the presence of plaque and inflammation in the loci of deep pockets could be a prognostic factor for disease progression more accurate than PD alone; however, data from a 5-year randomized clinical trial (RCT) failed to demonstrate any association between peri-implantitis progression and clinical variables including plaque, BoP, and PD [31].

In the present analysis, direct comparisons among treatment groups were voluntarily avoided due to the high heterogeneity of available articles for inclusion criteria and re-treatment in the case of disease recurrence in the follow-up period. As for the inclusion criteria, most of the studies were designed before the publication of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. Therefore, their inclusion criteria follow different, more permissive, enrollment processes [17–21]. Following the directions of workgroup four of the 2017 World Workshop, peri-implantitis is diagnosed with: (i) presence of bleeding and/or suppuration on gentle probing. (ii) Increased probing depth compared to previous examinations. (iii) Presence of bone loss beyond crestal bone level changes resulting from initial bone remodeling, (iv) or with probing depths of ≥6 mm and bone levels ≥3 mm apical of the most coronal portion of the intraosseous part of the implant in the case of absence of baseline data. [1].

Another point of disagreement among authors is whether or not implants should be retreated during the follow-up in the case of disease recurrence. Roccuzzo et al. and Isehed et al. surgically retreated implants in the case of disease recurrence and provided data mixing those treated once with those treated more than once [9,14]. On the other hand, Schwarz et al. excluded retreated implants from the main statistical analysis [13,32]; similarly, Romeo et al. dismissed patients showing persistence of inflammation [36].

The large heterogeneity of existing studies might be used as a call to suggest more unitary directions for future research studies. Standardized inclusion criteria following the 2017 World Workshop appear to be of primary importance. In addition, authors should report data of implants not responding to the treatment with separate analyses, to increase the focus of literature on possible negative prognostic factors after treatment of peri-implantitis.

5. Conclusions

In the light of the discussed heterogeneity, surgical treatment of peri-implantitis following flap, resective or regenerative approaches improved peri-implant probing depth and survival rate three to seven years after surgical treatment of peri-implantitis. Regenerative therapies induced more favorable radiographic bone gain and biological outcomes.

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