Regenerative Treatment of Peri-Implantitis: A Systematic Review

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**Article Info**

**A B S T R A C T**

**Objectives:** The aim of this systematic review was to assess the clinical efficacy of bone regeneration for treatment of peri-implantitis.

**Materials and Methods:** Electronic search of the literature was performed to identify randomized clinical trials (RCTs) and case series on treatment of peri-implantitis using bone regeneration procedures with at least 6 months of follow-up. The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) were applied. The risk of bias was assessed using the Cochrane Collaboration’s Risk of Bias tool.

**Results:** Two RCTs and 16 case series with a total of 520 treated patients (2002 implants) were included. Bone regenerative procedures showed controversial results regarding bone fill. Two studies reported statistically significant bone gain while four studies reported insignificant bone gain. Other studies reported bone gain with no P value. Pocket depth (PD) reduction varied among the studies since four studies reported a significant reduction in PD while four others reported insignificant reduction in PD. Other studies reported a reduction in PD with no P value. Bone regenerative procedures seemed to decrease bleeding on probing (BOP) but they did not seem conducive to increase the width of keratinized gingiva. Increased keratinized gingiva was noted in cases with subepithelial grafts.

**Conclusion:** Evaluation of the effectiveness of bone regeneration techniques in this systematic review presented limitations related to heterogeneity in patient selection (age, history of periodontitis, smoking status and implant system), means of disinfection and decontamination, and variability of the materials used for treatment.

**Keywords:** Peri-Implantitis; Dental Implantation, Endosseous; Dental Implants; Guided Tissue Regeneration

**INTRODUCTION**

Peri-implantitis is characterized by an inflammatory process around the implant, which includes both soft tissue inflammation and progressive loss of the supporting bone exceeding biological bone remodeling [1,2]. Recent studies and reviews have reported the prevalence of peri-implantitis to be 2.7% to 47.1% [3-7]. Success rates <70% have been reported in high-risk groups such as patients with a previous history of treated periodontitis and smokers [8-11]. Although non-surgical periodontal therapy including mechanical debridement in combination with local antibiotics or laser application as an adjunct have been reported to effectively prevent the progression of peri-implantitis, beneficial clinical outcomes only occur within a period of 6 to 12 months [12-16]. Reinfection of a previous defect area is most
probably due to the inability of non-surgical surface debridement to completely remove bacterial deposits from the structured titanium implant surfaces; thus, lacking a new bone-to-implant contact at the histological level [17]. Regenerative surgical treatments including the use of bone grafts have demonstrated clinical and radiographic improvements over a 3-year-period [18]. Khoury and Buchmann [18] employed combinations of bone grafts/bone substitutes and membranes and reported clinical and radiographic improvements over 3 years. The aim of this study was to systematically review the outcome of reconstructive surgical procedures using bone graft substitutes with or without a membrane to treat bone defects due to peri-implantitis based on peri-implant probing pocket depth (PD), bleeding on probing (BOP) and marginal bone loss.

MATERIALS AND METHODS
A detailed protocol was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19]. The present manuscript was written according to the PRISMA checklist.

Information sources and search strategy
Literature search was conducted in electronic databases namely MEDLINE (PubMed), Cochrane and EBSCO until September 2017 to identify relevant studies. The search was performed independently by two authors (A.K. and R.Y.). The searched terms were as follows: “peri-implantitis” [mh] OR “periimplantitis” [ti] OR (“dental implantation, endosseous” [mh] OR “dental implants” [mh]) AND (“peri implant” [tiab] OR “peri-implantitis” [tiab]) AND (regeneration [tiab] OR regenerative [tiab] OR “guided tissue regeneration” [mh] OR surgery [ti] OR surgical [ti] OR “bone graft” [ti] OR “bone grafts”[ti]) AND English[la] NOT (letter [pt] OR comment [pt] OR editorial [pt]).

Eligibility criteria
The inclusion criteria were as follows:
- Randomized clinical trials (RCTs) or case series with the following characteristics:
- Interventions using membrane and bone graft substitutes/control groups treated without guided bone regeneration techniques.
- Interventions using bone graft substitutes, Emdogain /control groups treated without guided bone regeneration techniques.
- One guided bone regeneration procedure for treatment of peri-implantitis
- At least 6 months of study duration
- Articles had to be conducted in the past 10 years
- Only cases of treatment of bone defects due to marginal peri-implantitis were considered.
- The exclusion criteria were as follows:
- Studies dealing with peri-apical peri-implantitis due to its different etiology and therapeutic approaches
- Conventional treatments
- Cross-sectional studies, case reports and animal studies.

Selection
Criteria used in this systematic review for study selection were based on the PICO method, according to the following points:
Type of participants:
Patients with a clinical diagnosis of peri-implantitis (bone defects, probing PD > 5 mm with/or without BOP)
Type of interventions:
Guided bone regeneration procedures (using bone graft and membrane or bone graft alone or enamel matrix derivative) for treatment of peri-implantitis were considered.
Comparison between interventions:
All possible comparisons between the included surgical procedures were investigated.
Type of outcome measures:
The following outcome measures were considered:
- Defect fill expressed as bone gain (mm) at the follow-up visit
- Probing PD reduction (mm) at the follow-up visit
- Recession reduction: Change in gingival recession (mm) at the follow-up visit
- Keratinized tissue gain: Change (mm) in width of keratinized tissue at the follow-up visit
- BOP expressed as BOP reduction (%) at the follow-up visit
- Plaque index (PI) expressed as PI reduction at the follow-up visit
Assessment of quality and risk of bias
Three main quality criteria were examined: allocation concealment, blinding of outcome assessors, and completion of follow-up. After quality assessment, studies were grouped into three categories:

- Low risk of bias, if all three quality criteria were met
- Unclear risk of bias, if one or more criteria were partially met
- High risk of bias, if one or more of the three quality criteria were not met.

This evaluation was performed independently by two authors (A.K. and R.Y.) according to the Cochrane Handbook for Systematic Reviews of Interventions [20].

Data abstraction
The following information was extracted independently by two authors (A.K. and R.Y.). The extracted data included title, authors’ names, year of publication, study design, number of participants, outcome measures, type of intervention, duration of study, clinical outcomes, and study quality.

RESULTS

Study selection
The search results are presented in Figure 1. The electronic search in MEDLINE (PubMed), Cochrane Collaboration databases, and EMBASE provided 359 articles published between 2007 and 2017. Subsequently, after reading all the abstracts and eliminating the duplicates, 29 articles were selected. The full texts of the 29 articles were read and allowed selection of 18 studies that met the inclusion criteria of this systematic review.

Study characteristics
Included studies:
Two RCTs, 14 prospective case series, 1 prospective case series cohort and 1 retrospective study were included in this systematic review (Table 1).
Table 1. Characteristics of the included studies

| Reference                  | Study Design       | Type of study | Subject/implant | Patient information | Intervention | Intervention |
|----------------------------|--------------------|---------------|-----------------|---------------------|--------------|--------------|
| Schwarz et al, 2009 [26]   | 4 years            | Prospective cases series | Group 1:9 | 54.4±12.5 | CAM, ITI, KSI, MTX, TSV, ZL | Debridement: removal of granulation tissue (plastic curettes) | Group 1: Nanocrystalline hydroxyapatite Group 2: Natural bone mineral + collagen membrane |
|                            |                    |               | Group 2: 11 | ND | BRA CAM, ITI, KSI, MTX, TSV, ZL | Decontamination: saline solution, subgingival irrigation with 0.2% CHX |
| Roos-Jansåker et al, 2011 [23] | 3 years            | Prospective case series | Group 1: 15/27 | 65.5±7.4 | BRA, ASTRA | Debridement: removal of granulation tissue Decontamination: 3% hydrogen peroxide, saline solution ATB: amoxicillin 375 mg, 3/day and metronidazole 400 mg, 2/D, for 10 days, 0.1% CHX, ATI |
|                            |                    |               | Group 2: 17/29 | 66.3±6.3 | 70.6 | |
| Parma-Benfenati et al, 2015 [30] | 22 months         | Prospective cases series | 6/9 | 48-63 | TiO² TPS SLA Machined | Debridement: removal of granulation tissue (US, Ti curettes, titanium toothbrush) Decontamination: air powder abrasive, photodynamic therapy, tetracycline |
|                            |                    |               |                | 1 | NR | |
| Froum SJ et al, 2012 [31]  | 3-7.5 years        | Prospective cases series | Group 1: 15/19; greatest defect depth visible on X-ray | 29-81 | NBL Zi BH St BI Astra Fr In | Debridement: removal of granulation tissue Decontamination: air powder abrasive, saline solution, tetracycline, CHX, EMD |
|                            |                    |               | Group 2: 23/32; greatest bone loss on facial or lingual implant aspect | | | • Bone graft + Platelet-derived growth factor • Subepithelial connective tissue graft or resorbable membrane |
| Authors          | Year(s) | Study Design   | N (Successful/Total) | Mean Bone Graft (±SD) | % Success | Bone/Soft Tissue Grafts and Procedures |
|------------------|---------|----------------|----------------------|-----------------------|-----------|---------------------------------------|
| Schwarz et al, 2014 | 6 months | Prospective cases series | 10/13 | 55.8±16.6 | NR | BRA, CAM, ITI, TSV, NI Debridement: removal of granulation tissue (universal curettes), Er:YAG laser; Exposed threads were smoothened using diamond burs and Arkansas stones Decontamination: saline solution |
| Froum SJ et al, 2014 | 1 year | Prospective cases series | 5/12 | NR | NR | NR Debridement: granulation tissue removal (curettes Ti, titanium toothbrush) Decontamination: air powder abrasive, saline, CHX, tetracycline |
| Roos-Jansåker et al, 2014 | 5 years | Prospective cases series | Group 1: 13/23 bone graft+ resorbable membrane 64.9±7.5 | 12% | BRA, 1 Astra Debridement: removal of granulation tissue Decontamination: 3% hydrogen peroxide, saline solution, ATB |
| Froum SJ et al, 2015 | 2-10 years | Prospective cases series | 100/170 | 20 – 83 | 19 | NR Debridement Decontamination: tetracycline, 0.12% CHX, saline spray, air powder abrasive |
| Romanos et al, 2008 | 27±17,83 months | Prospective cases series | 15/19 | 57.21±12.14 | NR | Ankylos, ITI, IMZ, Debridement: removal of granulation tissue (Ti curettes) Decontamination |
| Matarasso et al, 2014 | 1 year | Prospective cases series | 11/11 | 63.6±8.9 | 5 | NR Debridement: removal of granulation tissue (Ti curettes) The part of the implant located in the suprabony compartment of the defect was planed and polished with burs. |

- Bone graft
- Subepithelial connective tissue graft or membrane
- EMD ± PDGF
- Bone allograft
- Subepithelial connective tissue graft
- Bone graft mixed with blood ± resorbable membrane
- Mineralized freeze-dried bone &/or anorganic bovine bone combined with PDGF or EMD
- Resorbable membrane &/or subepithelial connective tissue graft
- Autogenous bone graft (n=10)
- Xenogeneic bone graft (Bio-Oss, n=9)
- Collagen membrane
- Deproteinized bovine bone mineral
- Collagen membrane
The implant surface located in the intrabony defect was debrided with glycine powder, saline solution.

### Roos-Jansson et al., 2007 [21]

| Year | Study Design | Cases | Healing | Debridement | Decontamination |
|------|--------------|-------|---------|-------------|----------------|
| 1 year | Prospective cases series | 12/16 | 64.4±6.0 | 10 BRA | Bone substitute, Resorbable membrane, Submerged healing |
| 6 months | Prospective cases series cohort | Group 1: 17/29, bone substitute mixed with blood + resorbable membrane | 65±7.4 | 16 BRA, 1 Astra | Bone substitute mixed with blood, Resorbable membrane |

### Arab et al., 2016 [36]

| Year | Study Design | Cases | Healing | Debridement | Decontamination |
|------|--------------|-------|---------|-------------|----------------|
| 6 months | Prospective cases series | 10/24 | NR | NR | Bone graft: Porous titanium granule or autogenous, or Bio-Oss membrane |

### Schwarz et al., 2015 [37]

| Year | Study Design | Cases | Healing | Debridement | Decontamination |
|------|--------------|-------|---------|-------------|----------------|
| 8 months - 6,5 years | Retrospective of 5 cases | 5/5 | NR | NR | Bone xenograft (Bio-Oss), Collagen membrane (double layer) |

### Isehed et al., 2016 [25]

| Year | Study Design | Cases | Healing | Debridement | Decontamination |
|------|--------------|-------|---------|-------------|----------------|
| 12 months | Randomized clinical trial | EMD: 12 | 61-81 | 26.7 | Nobel turned Nobel TiUnite Astra, SLA, 3iStraumann |
| NO EMD: 13 | | 67-83 | 42.9 | | Application of 0.3 ml Emdogain |
| Study | Time | Type | Cases | M/C | Treatment |
|-------|------|------|-------|-----|-----------|
| Wiltfang et al, 2012 [38] | 12 months | Prospective cases series | 22/36 | 24-83 | Debridement: removal of granulation tissue, Decontamination: etching gel, local rinsing |
| Rocuzzo et al, 2016 [29] | 12 months | Prospective cases series | 75/75 | 57.8-8.5 | 11 | Straumann, Dental Implant System, Straumann, AG, Scaling and root planing of teeth and cleaning of implant shoulders, oral hygiene instructions Debridement: Removal of granulation tissue (Ti curettes, titanium brush) Decontamination of implant by etching gel, 1% CHX gel |
| Jepsen et al, 2016 [28] | 12 months | Prospective multicenter, multinational randomized | Test (PTGs; n=33) | 57.7±12.6 | 20 | Ankylos Astra (OsseoSpeed) Dyna Friadent Xive Nobel Biocare Sic Invent 1Straumann (standard neck) Tri-MAX TMI Zimmer Biomet 3i Oral hygiene instructions, Nonsurgical periodontal/peri-implantation, and surgical periodontal therapy |
| | | | | | | Oral flap debridement alone |
| | | | | | | Open flap debridement + PTG |

CAM: Camlog Screw Line®, ITI®, ITI,® KSI; KSI Bauer Schraube®, MTX: Spline Twist®, TSV: Tapered Screw vent®, ZL: ZL-Durapent (ticer)®, BRA: Branemark System®, NBL: Nobel Biocare, Zi: Zimmer, BH: BioHorizons, ST: Straumann, B: Biomet, Astra: AstraTech, IN: Innova, FR: Frialit, CAM: Camling Screw Line®, TSV: Tapered Screw Vent®, Ankylos, ITI: ITI®, Ni: not identifiable Implant system. NH: Nanocrystalline hydroxyapatite, NBM: naturel mineral bone, CM: collagen membrane, TiO²: titanium oxide surface, TPS: titanium plasma-sprayed surface. SLA: sandblasted and acid-etched surface. EMD: Emdogain®, CHL: Chlorohexidine, ATB: antibiotics, ATI anti-inflammatory: anti-PDGF: platelet-derived growth factor, PTG: porous titanium granules.
Among the included studies:

- Five studies [21-25] were completely supported by public institutes for research.
- One study [26] was supported, in part, by companies whose products were used for the interventions in the trial and by public institutes for research.
- Two studies [27,28] were supported, in part, by companies whose products were used for interventions in the trials.
- One study [29] was self-funded.
- Nine studies [30-38] did not report how the study was supported.

Excluded studies:

Eleven studies were excluded for the following reasons:

- Impact of oral hygiene, severe periodontitis, severe marginal bone loss around the implant and poor compliance [39].
- Impact of presence or absence of pus [40]
- Case reports [40-42]
- Impact of implant configuration or design [43,44]
- Impact of “new cross-linked membrane” on management of peri-implant tissue before implant insertion [45]
- Evaluation of 2 methods of decontamination [46]
- Management of peri-implant tissue [47]
- Effect of conventional surgery [48]

**Risk of bias in included studies**

The quality assessment of included studies showed that only 2 RCTs were rated with low risk of bias [25,28]. The assessment of risk of bias is summarized in Table 2.

**Results of analysis**

Clinical outcomes from 2 RCTs and 16 case series on 520 patients and 2,002 treated peri-implantitis sites were included in this systematic review. The results can be summarized as follows:

- Regarding bone fill, only 2 studies [28,35] reported a significant bone gain while 5 studies [22-25,36] reported insignificant bone gain.
- Other studies reported bone gain but did not specify the P value.
- Bone regeneration procedures seemed to permit reduction of PD, varying from study to study and even from case to case; 4 studies [27,29,34,35] reported a significant reduction of PD while 4 other studies [22,24,25,36] reported insignificant reduction of PD. However, in other studies, the reduction of PD was reported without mentioning a P value.
- No improvement in recession and clinical attachment level
- Bone regeneration procedures seemed to reduce BOP; 4 studies [27, 29, 34, 35] reported a significant reduction in BOP while four other studies [26,31,33,36] showed a reduction in BOP without mentioning a P value.
- Bone regeneration procedures did not seem to increase the gingival keratinized tissue.

The results for bone fill, PD, recession, BOP, clinical attachment level gain, PI change and keratinized tissue gain are reported in Table 3.

**DISCUSSION**

The aim of this systematic review was to assess the clinical efficacy of bone regeneration procedures in treatment of peri-implantitis. Clinically, these lesions are characterized by a positive BOP, which is commonly associated with suppuration, a probing PD of 4.4 mm, and radiographic bone loss. In this systematic review, less attention was paid to crucial clinical parameters such as BOP and PD. These parameters were rarely reported. This is in contrast to the recommendations of the American Academy of Periodontology and the European Workshop on Periodontology which explicitly call for the data collection of BOP and PD in examination of peri-implantitis cases [49,50].

We defined bone regeneration procedures as procedures using

- Only resorbable or non-resorbable membranes [51-53]
- Membrane and bone grafts [54]
- Tissue engineering without membrane:
Table 2. Risk of bias assessment

| Study                          | Randomization | Allocation concealment | Examiner blinding | Completion of follow-up                                                                 | Risk of bias |
|-------------------------------|---------------|------------------------|-------------------|-----------------------------------------------------------------------------------------|--------------|
| Schwarz et al, 2009 [26]      | No            | No                     | No                | No (2 patients discontinued from NHA)                                                   | High         |
| Roos-Jansåker et al, 2011 [23]| No            | No                     | No                | No (6 patients discontinued from 38 patients)                                           | High         |
| Parma-Benfenati et al, 2015 [30]| No          | No                     | No                | Yes                                                                                     | High         |
| Froum et al, 2012 [31]        | No            | No                     | No                | Yes                                                                                     | High         |
| Schwarz et al, 2014 [27]      | No            | No                     | No                | Yes                                                                                     | High         |
| Froum et al, 2014 [32]        | No            | No                     | No                | Yes                                                                                     | High         |
| Roos-Jansåker et al 2014 [24] | No            | No                     | No                | No (12 patients discontinued from 38 patients)                                           | High         |
| Froum et al, 2015 [33]        | No            | No                     | No                | No (2 implants lost from 170 implants)                                                  | High         |
| Romanos et al, 2008 [34]      | No            | No                     | No                | Yes                                                                                     | High         |
| Matarasso et al, 2014 [35]    | No            | No                     | No                | Yes                                                                                     | High         |
| Roos-Jansåker et al, 2007 [21]| No            | No                     | No                | Yes                                                                                     | High         |
| Roos-Jansåker et al, 2007 [22]| No            | No                     | No                | No (2 patients discontinued from 38 patients in group 1)                                | High         |
| Arab et al, 2016 [36]         | Yes           | No                     | Yes               | No (2 patients discontinued from 10 patients)                                           | High         |
| Schwarz et al, 2015 [37]      | Yes           | No                     | Non               | No (2 cases of reinfection)                                                             | High         |
| Isehed et al, 2016 [25]       | Yes           | Yes                    | Yes               | No (2 cases of reinfection, 1 case discontinued and 1 implant lost)                     | Low          |
| Wiltfang et al, 2012 [38]     | No            | No                     | No                | No                                                                                     | High         |
| Roccuzzo et al, 2016 [29]     | No            | No                     | No                | No                                                                                     | High         |
| Jepsen et al, 2016 [28]       | Yes           | Yes                    | Yes               | No (12 patients lost from the control group)                                            | High         |
Table 3. Treatment outcomes

| Comparison                          | Defect fill (diff. in mm) | Probing depth (diff. in mm) | Recession (diff. in mm) | Clinical attachment level (diff. in mm) | Bleeding on probing (diff. %) | Plaque index (diff.) | Keratinized tissue (diff. in mm) |
|------------------------------------|---------------------------|-----------------------------|-------------------------|----------------------------------------|-----------------------------|---------------------|-----------------------------|
| **Schwarz et al, 2009 [26]**       |                           |                             |                         |                                        |                             |                     |                             |
| Gp1: NHA                           | NR                        |                             | 1.1±0.3                 | -0.5±0.2                               | 32                          | 0.5±0.2             | NR                          |
| Gp2: NBM + CM                      | NR                        |                             | 2.5±0.9                 | -0.5±0.3                               | 51                          | 0.2±0.3             | NR                          |
| P-value                            | NR                        | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| **Roos-Jansåker et al, 2011 [23]** |                           |                             |                         |                                        |                             |                     |                             |
| Group 1: Only bone substitute      | 1.3±1.3                   | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| Group 2. Bone substitute + resorbable membrane | 1.6±1.2                   | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| P-value                            | 0.40                      | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| **Parma-Benfenati et al, 2015 [30]** |                           |                             |                         |                                        |                             |                     |                             |
| Patient No. 1: non submerged + resorbable membrane | 5                         | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| Patient No. 2: submerged + resorbable membrane | 5                         | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| Patient No. 3: submerged + resorbable membrane | 2                         | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| Patient No. 4: submerged + nonresorbable membrane | 5                         | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| Patient No. 5: submerged + nonresorbable membrane | 6                         | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| Patient No. 6: submerged + nonresorbable membrane | 8                         | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| Patient No. 7: submerged + nonresorbable membrane | 3                         | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| Patient No. 8: submerged + nonresorbable membrane | 7                         | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| Patient No. 9: submerged + nonresorbable membrane | 4                         | NR                          | NR                      | NR                                     | NR                          | NR                  | NR                          |
| Study/Method | Group 1 | Group 2**probing bone | Schwarz et al., 2014 [27] | Group 1: bone graft + resorbable membrane | Group 2: only bone graft | Romanos et al., 2008 [34] | Matarasso et al., 2014 [35] |
|-------------|---------|-----------------------|-----------------------------|-------------------------------|------------------------|---------------------------|-------------------------------|
|             | 3.75    | 5.4±1.5               | NR                          | 75.50±1.4±1.5                 | 45%                    | 8.0±3.7                   | Before (bone level)            |
|             | 3.00*   | 5.1±1.9               | NR                          | 15.265±1.0±1.2                | NR                     | 5.2±3                     | After (bone level)             |
|             |         |                       | Autogenous bone graft +     |                               |                        |                           | Before                         |
|             |         |                       | resorbable membrane         |                               |                        |                           | After                          |
|             |         |                       | P-value (within group, paired t-test) |                               |                        |                           | Before                         |
|             |         |                       | NR                          |                               |                        |                           | After                          |
|             |         |                       | 2.53±1.80                   | -0.46±0.77                    | 74.39±28.52            | 101±1.37                  | Before (bone level)            |
|             |         |                       | -0.77                       | 2.07±1.93                     | 2.48±0.63              | 0.98±1.2                  | After                          |
|             |         |                       | 74.39±28.52                 |                               |                        |                           | Before                         |
|             |         |                       | 0.23±0.5                    |                               |                        |                           | After                          |
|             |         |                       | 75.4±1.5                    |                               |                        |                           | NR                            |
|             |         |                       | 0.19                        |                               |                        |                           | NR                            |
|             |         |                       | 45%                         |                               |                        |                           | NR                            |
|             |         |                       | NR                          |                               |                        |                           | NR                            |
|             |         |                       | NR                          |                               |                        |                           | NR                            |
|             |         |                       | 6.30±1                       |                               |                        |                           | NR                            |
|             |         |                       | 2.48±0.63                   |                               |                        |                           | NR                            |
|             |         |                       | 0.98±1.2                    |                               |                        |                           | NR                            |
|             |         |                       | 2.41±1.39                   |                               |                        |                           | NR                            |
|             |         |                       | 0.23±0.5                    |                               |                        |                           | NR                            |
|             |         |                       | 0.19                        |                               |                        |                           | NR                            |
|             |         |                       | 45%                         |                               |                        |                           | NR                            |
|             |         |                       | NR                          |                               |                        |                           | NR                            |

Note: NR = Not reported/Not applicable.
| Study/Group | Description | Mean ± Standard Deviation | P-value (initial state vs follow-up visits) | P-value (difference between groups) |
|-------------|-------------|---------------------------|-------------------------------------------|--------------------------------------|
| **Roos-Jansåker et al, 2007 [21]** | Bone graft (non-bovine derivative) mixed with blood | 2.3±1.2 | -2.8±1.4 | 1.4±1.7 | NR | NR | NR |
| | Resorbable membrane | 4.2±1.5 | -1.2±1.5 | 1.59±2.0 | NR | NR | NR |
| **Roos-Jansåker et al, 2007 [22]** | Group 1: Bone graft mixed with blood + resorbable membrane | 1.52±1.16 | -1.28±1.51 | 1.59±2.0 | NR | NR | NR |
| | Group 2: Bone graft alone | 1.44±1.27 | -1.61±1.61 | 1.8±1.37 | NR | NR | NR |
| | P-value (difference between initial state and follow-up visits) | 0.8 | 0.4 | 0.6 | NR | NR | NR |
| **Arab et al, 2016 [36]** | Group 1: Bone graft alone: titanium porous granules | 0.85 ± 1.06 | 1.1 ± 1.4 | -1.1 ± 2.1 | 18.1 | NR | NR |
| | Group 2: Bone graft (bovine mineral bone) + resorbable membrane | 1.4 ± 1.04 | 2.4 ± 1 | -2.4 ± 1.3 | -50 | NR | NR |
| | P-value (difference between the 2 groups) | 0.251 | 0.084 | 0.512 | NR | NR | NR |
| **Schwarz et al, 2015 [37]** | Case 1 | 3.25 ± 1.26 | NR | NR | NR | NR | NR |
| | Case 2 | 3 ± 1.41 | NR | NR | NR | NR | NR |
| | Case 3 (reinfection of mesial aspect) | 3.33 ± 1.53 | NR | NR | NR | NR | NR |
| | Case 4 | 3 ± 1 | NR | NR | NR | NR | NR |
| | Case 5 (reinfection of mesial and distal aspects) | 1.0 ± 1.41 | NR | NR | NR | NR | NR |
| | Mean ± std. deviation (excluding infected sites) | 3.52 ± 0.88 | NR | NR | NR | NR | NR |
| **Isehed et al, 2016 [25]** | EMD | 0.9 | 2.8 | NR | NR | NR | NR |
| | NO EMD | -0.1 | 3.00 | NR | NR | NR | NR |
| | P-value | 0.295 | 0.270 | NR | NR | NR | NR |
| Study            | Treatment                                                                 | Postop Gain (mm) ± SD | Preop Gain (mm) ± SD | P-value          | Postop Gain (mm) ± SD | Preop Gain (mm) ± SD | P-value          | Postop Gain (mm) ± SD | Preop Gain (mm) ± SD | P-value          |
|------------------|---------------------------------------------------------------------------|-----------------------|----------------------|------------------|-----------------------|----------------------|------------------|-----------------------|----------------------|------------------|
| Wiltfang et al., 2012 [38] | Autogenous + xenogeneic bone graft Without membrane | 3.5 ± 2.4              | 4.0 ± 1.8             | NR               | 36                    | NR                   | NR               | 2.92 ± 1.73           | NR                   | NR               |
| Roccuzzo et al., 2016 [29]   | Deproteinized mineral bovine bone + 10% collagen without membrane         | NR                    | 2.92 ± 1.73           | NR               | 53.2 ± 39.4           | NR                   | NR               | NR                    | 4.2 ± 26.4           | 0.58 ± 1.24      |
| Jepsen et al., 2016 [28]     | Test group: PTG + surgery conventional (mesial/distal) Control group: Conventional surgery alone (mesial/distal) | 3.61 / +3.56          | 2.8 ± 1.3             | NR               | NR                    | NR                   | NR               | NR                    | NR                   | NR               |
|                              | P-value (statistical difference between groups)                            | <0.0001               | 2.6 ± 1.4             | NS               | NR                    | NR                   | NR               | <0.0001               | NR                   | 0.15             |

NHA: Nanocrystalline hydroxyapatite; NBM: Natural bone mineral; NR: Not reported; Diff.: Difference between pre-op and postop; EMD: Emdogain; PTG: Porous titanium granules; NS: non-significant
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- Bone xenografts and bone autografts [38] or bone xenografts and 10% collagen [29]
- Porous titanium granules [28]
- Enamel matrix derivative (Emdogain) [25]

Guided bone regeneration is similar to guided tissue regeneration. Osseous regeneration by guided bone regeneration depends on the migration of pluripotent and osteogenic cells (e.g. osteoblasts derived from the periosteum and/or adjacent bone and/or bone marrow) to the bone defect site and exclusion of cells impeding bone formation (e.g. epithelial cells and fibroblasts) [51-53,55].

**Bone fill (mm):**
Bone regeneration procedures remain a controversial topic in terms of bone fill. The bone gain varied from 1.1 mm to 3.56 mm. The results of this review seemed to be in accordance with a systematic review [56] and a meta-analysis [57] that concluded that a complete fill of the bony defects caused by peri-implantitis using a guided bone regeneration protocol did not seem to be a predictable outcome. A partial defect fill can be expected. A meta-analysis [57] concluded that the mean bone fill was 2.17 mm.

**Periodontal PD (mm):**
Bone regeneration procedures seemed to allow reduction of PD, varying from study to study. The reduction in PD varied from 1.1 mm to 5.4 mm. In a systematic review [56], there were no data given for PD after surgery, but in some cases it was possible to calculate it by subtracting the PD after treatment from the PD measured before treatment. This value served for estimating the mean value of the residual PD of 3.23 mm post-treatment. A meta-analysis [57] seemed to be in accordance with the present review, and showed a reduction of PD varying from study to study without mentioning whether it was statistically significant or not. It was concluded that the mean reduction was 2.97 mm.

**Recessions (mm):**
There was a shortcoming in soft tissue evaluation. A meta-analysis [57] reported that the results varied from one study to another. Increased recessions were reported in some studies and decreased recessions were reported in others.

**Clinical attachment level (mm):**
Almost all of the studies reported a PD reduction with regenerative procedures. In a meta-analysis [57], only few studies reported information about clinical attachment level; in those studies, the clinical attachment gain was obtained (mean of 1.65 mm) without mentioning if it was statistically significant.

**BOP (%):**
Bone regeneration procedures seemed to reduce BOP. In a systematic review [56], most studies reported reduction in BOP without mentioning the P-value and only two studies reported absence of BOP. A meta-analysis [57] showed that most of the studies did not report information about BOP.

**Keratinized gingiva (mm):**
Bone regeneration procedures did not seem to increase keratinized gingival tissue. An increase in gingival keratinized tissue was obtained, only when subepithelial gingival graft was used. A systematic review [56] and a meta-analysis [57] did not report any data on the change in the height of the keratinized tissue.

**Study limitations:**
The studies reviewed here used a number of different implant systems with varying fixture designs and surfaces combined with different bone graft substitutes and barrier membranes. Therefore, comparison of different peri-implant surgery cases was not accurately feasible. The variety of methods to decontaminate implant surfaces are also factors that may explain the variability in defect fill among the included studies. The observation periods in the included studies ranged from 6 months to 5 years, and reexamination intervals varied greatly. Long-term follow-up examinations are required for a more valid assessment.

The reasons for marginal peri-implant bone loss can be diverse. It may have different etiologies, such as infection, inappropriate occlusal contact, and mechanical problems. In addition, soft tissue thickness plays a central role in resistance to the inflammatory processes. It is therefore difficult to compare studies when these data are not recorded.

There are no RCTs available to compare the
clinical effectiveness of bone regeneration and other procedures. Consequently, studies with a lower level of evidence, such as case series and patient cohorts from RCTs with different aims, were included in order to benefit from the available data in the literature and to investigate the possible differences. The quality of data presentation is also a problem. The P-values had not been reported in most studies. Thus, it was difficult to attest if the differences were statistically significant. Most studies did not use all clinical and radiographic parameters to evaluate the effectiveness of peri-implantitis treatment. It is noteworthy that inclusion of a large number of smokers and patients with systematic diseases and history of periodontitis might have contributed to the unfavorable outcomes observed.

CONCLUSION

- A complete fill of bone defects caused by peri-implantitis using a guided bone regeneration protocol does not seem to be a predictable outcome. Only a partial defect fill can be expected.
- Bone regeneration procedures seem to allow a reduction in PD and BOP.
- There was a shortcoming in soft tissue evaluation. But some studies reported augmentation of recessions.
- Bone regeneration procedures do not seem to increase gingival keratinized tissue unless accompanied by a subepithelial gingival graft.

The evaluation of bone regeneration techniques requires:

- RCTs comparing different varieties of bone regeneration techniques or comparing bone regeneration techniques with other approaches
- Multicenter studies when it is necessary to:
  - Specify the origin of peri-implantitis (mechanical or infectious)
  - Use a single method of detoxification and decontamination allowing comparisons between studies
  - Using the same radiographic and clinical parameters and the same duration of follow-up in the diagnosis and evaluation of interventions
- Present results by reporting changes between baseline and follow-up visits
- Use a single type of biomaterial for tissue engineering and the same type of membrane allowing comparisons between studies
- Use statistical tests (with P value) to compare the studied parameters
- Selection of patients (inclusion criteria): taking into consideration the history of periodontitis, smoking status, age, general condition, and the implant system used.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interests affecting any author.

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