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Regenerative Treatment of Peri-Implantitis: A Systematic Review

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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 regeneration 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

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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

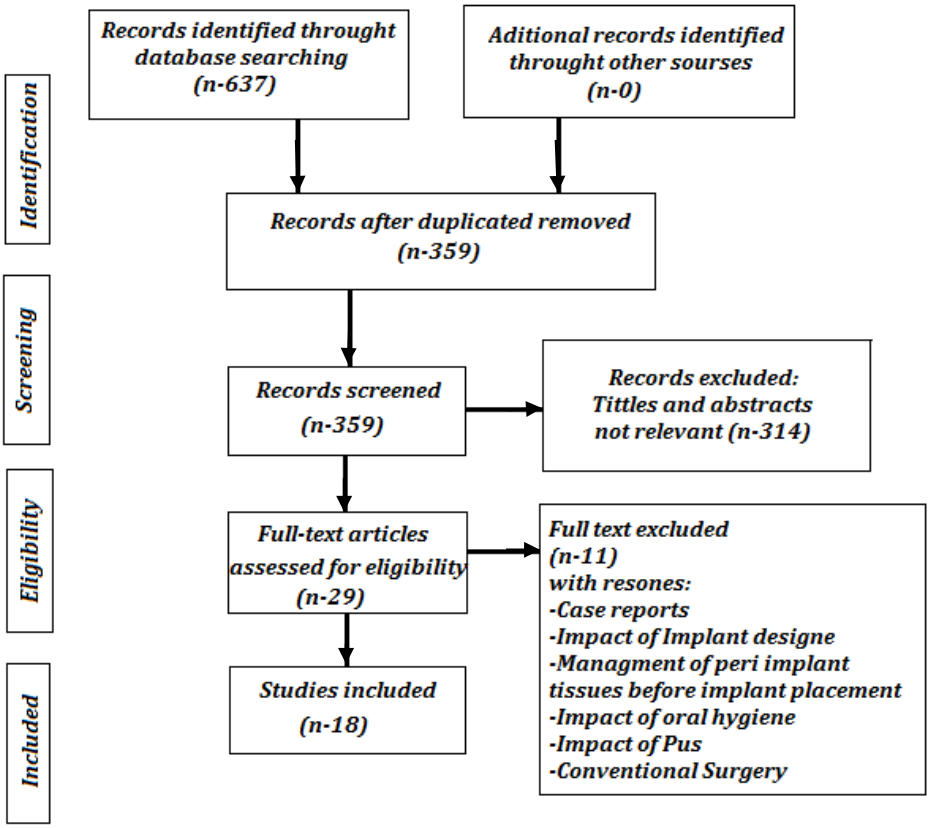

Fig. 1. PRISMA flow diagram of article screening and selection process

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 earch 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		Patient information			Intervention	
	Follow-up	Type of study	Subject/ implant	Age (y)	Smoker (%)	Type of implant	Before intervention	Intervention
Schwarz et al, 2009 [26]	4 years	Prospective cases series	Group 1:9 Group 2: 11	54.4±12.5	ND ND	CAM, ITI, KSI, MTX, TSV, ZL BRA CAM, ITI, KSI, MTX, TSV, ZL	Debridement: removal of granulation tissue (plastic curettes) Decontamination: saline solution, subgingival irrigation with 0.2% CHX	Group 1: Nanocrystalline hydroxyapatite Group 2: Natural bone mineral + collagen membrane
Roos-Jansåker et al, 2011 [23]	3 years	Prospective case series	Group 1: 15/27 Group 2: 17/29	65.5±7.4 66.3±6.3	68.4 70.6	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 1: Bone graft Group 2: Bone graft+ resorbable membrane
Parma-Benfenati et al, 2015 [30]	22 months	Prospective cases series	6/9	48-63	1	TiO^2 TPS SLA Machined	Debridement: removal of granulation tissue (US, Ti curettes, titanium toothbrush) Decontamination: air powder abrasive, photodynamic therapy, tetracycline	Membrane (resorbable or non resorbable)
Froum SJ et al, 2012 [31]	3-7.5 years	Prospective cases series	Group 1: 15/19; greatest defect depth visible on X-ray Group 2: 23/32; greatest bone loss on facial or lingual implant aspect	29-81	NR	NBL Zi BH St BI Astra Fr In	Debridement: removal of granulation tissue Decontamination: air powder abrasive, saline solution, tetracycline, CHX, EMD	• Bone graft + Platelet-derived growth factor • Subepithelial connective tissue graft or resorbable membrane

Schwarz et al, 2014 [27]	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	• Bone graft • Subepithelial connective tissue graft or membrane
Froum SJ et al, 2014 [32]	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	• EMD ± PDGF • Bone allograft • Subepithelial connective tissue graft
Roos-Jansåker et al, 2014 [24]	5 years	Prospective cases series	Group 1: 13/23 bone graft+ resorbable membrane Group 2: 12/22 bone graft alone	64.9±7.5 65.7±7.4	12% 11%	BRA, 1 Astra	Debridement: removal of granulation tissue Decontamination: 3% hydrogen peroxide, saline solution, ATB	• Bone graft mixed with blood ± resorbable membrane
Froum SJ et al, 2015 [33]	2-10 years	Prospective cases series	100/170	20 – 83	19	NR	Debridement Decontamination: tetracycline, 0.12% CHX, saline spray, air powder abrasive	• Mineralized freeze-dried bone &/or anorganic bovine bone combined with PDGF or EMD • Resorbable membrane &/or subepithelial connective tissue graft
Romanos et al, 2008 [34]	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	• Autogenous bone graft (n=10) • Xenogeneic bone graft (Bio-Oss, n=9) • Collagen membrane
Matarasso et al, 2014 [35]	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.	• Deproteinized bovine bone mineral • Collagen membrane

							The implant surface located in the intrabony defect was debrided with glycine powder, saline solution	
Roos-Jansåker et al, 2007 [21]	1 year	Prospective cases series	12/16	64.4±6.0	10	BRA	Debridement: removal of granulation tissue Decontamination: ATB, 3% hydrogen peroxide, saline	• Bone substitute • Resorbable membrane • Submerged healing
Roos-Jansåker et al, 2007 [22]	1 year	Prospective cases series cohort	Group 1: 17/29, bone substitute mixed with blood+resorb-able membrane Group 2: 19/36, bone graft alone	65±7.4 66.3±6.8	16 17	BRA, 1 ASTRA	Debridement: Removal of granulation tissue Decontamination: ATB, 3% hydrogen peroxide 3%, saline	• Bone substitute mixed with blood • Resorbable membrane
Arab et al, 2016 [36]	6 months	Prospective cases series	10/24	NR	NR	NR	Debridement: Removal of granulation tissue (carbon fiber curette and rubber cap polishing) Decontamination: air powder abrasive, saline, 0.2% CHX	• Bone graft: Porous titanium granule or autogenous, or Bio-Oss membrane
Schwarz et al, 2015 [37]	8 months - 6,5 years	Retrospective of 5 cases	5/5	Case 1: CI Ic Case 2: CI Ic Case 3: CI Ic Case 4: CI Ib Case 5: CI Ib	NR	NR	Debridement: Removal of granulation tissue (Universal curettes)+Implantoplasty (bucally and supracrestally >1 mm exposed implant parts) Decontamination: polishing and smoothening using burs and Arkansas stones under irrigation	• Bone xenograft (Bio-Oss) • Collagen membrane (double layer)
Isehed et al, 2016 [25]	12 months	Randomized clinical trial	EMD: 12 NO EMD: 13	61-81 67-83	26.7 42.9	Nobel turned Nobel TiUnite Astra, SLA, 3iStraumann	Debridement: removal of granulation tissue (UltraSons, Ti curettes) Decontamination: saline	• Application of 0.3 ml Emdogain

Wiltfang et al, 2012 [38]	12 months	Prospective cases series	22/36	24-83	ND	ND	Debridement: removal of granulation tissue, Decontamination: etching gel, local rinsing	• Bone graft (autogenous and xenograft) • Without membrane
Roccuzzo 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	• Deproteinized bovine bone graft with 10% collagen • If the area presented no keratinized tissue: use of a connective tissue graft
Jepsen et al, 2016 [28]	12 months	Prospective multicenter, multinational randomized	Test (PTGs; n=33) Control (OFD; *n*=30)	57.7±12.6 59.1±12.2	20 18	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	• Open 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, TIO^2: 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

	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	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	4 criteria : outcomes						
	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	-0.6±0.2	32	0.5±0.2	NR
Gp2: NBM + CM	NR	2.5±0.9	-0.5±0.3	-2.0±0.0	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
	5	NR	NR	NR	NR	NR	NR
Patient No. 4: submerged + nonresorbable membrane	6	NR	NR	NR	NR	NR	NR
Patient No. 5: submerged + nonresorbable membrane	8	NR	NR	NR	NR	NR	NR
Patient No. 6: submerged + nonresorbable membrane	3	NR	NR	NR	NR	NR	NR
	7	NR	NR	NR	NR	NR	NR
	4	NR	NR	NR	NR	NR	NR

Froum et al, 2012 [31]														
Group 1	3.75			5.4±1.5		NR		NR		21.5 (post-op)		NR	+1.3±1.4	
Group 2probing bone**	3.00*			5.1±1.9		NR		NR		15.265 (post-op)		NR	+1.0±1.2	
Schwarz et al, 2014 [27]														
Autogenous bone graft + resorbable membrane	NR			2.53±1.80		-0.46 ± 0.77		-2.07 ± 1.93		74.39±28.52		0.23±0.5	NR	
P-value *(within group, paired t-test)*	NR			0.000		0.076		0.003		0.00		0.19	NR	
Froum et al, 2014 [32]														
Bone allograft + autogenous bone graft	5.33			NR		NR		NR		NR		NR	NR	
Roos-Jansåker et al, 2014 [24]														
Group 1: bone graft + resorbable membrane	1.5±1.2			3.0±2.4		-1.3±1.7		-1.9±2.1		NR		45%	NR	
Group 2: only bone graft	1.1±1.2			3.3±2.0		-2.0±1.8		-2.2±2.4		NR		45%	NR	
P-value	0.24			0.60		0.50		0.38		NR		NR	NR	
Froum et al, 2015 [33]														
Xenogeneic bone graft + resorbable membrane	1.77±1.99			5.10±2.20		NR		NR		91.07		NR	+0.52±1.44	
Romanos et al, 2008 [34]														
Autogenous bone graft *(10 implants)*	0-2 mm; 0 1/3 implant length; 8		; 13 (nb) ; 6 (nb)	Before	After					Before	After		Before	After
Autogenous bone graft + Bio-Oss *(9 implants)* membrane	2/3 implant length; 7		; 0 (nb)	6.00± 2.03	2.48± 0.63	NR		NR		1.01±1.37	0.98±1.2	NR	2.30± 1.45	2.41± 1.39
	To apical area; 4		; 0 (nb)											
P-value *(within group)*	---------		------	<0.01		NR		NR		<0.01		NS	NS	
Matarasso et al, 2014 [35]														
Xenogeneic bone graft (Bio-Oss)	Before (bone level)	After (bone level)	Before	After	Before	After		Before	After	Before	After	NR	NR	
Resorbable membrane	8.0±3.7	5.2±3	8.1±1.8	4.0±1.3	1.7±1.5	3.0±1.8		9.7±2.5	6.7±2.5	19.7±40.1	6.1± 24	NR	NR	
P-value (difference between initial state and follow-up visits)	<0.001		0.001		0.003			0.001		0.032		NR	NR	

Roos-Jansåker et al, 2007 [21]							
Bone graft (non-bovine derivative) mixed with blood Resorbable membrane	2.3±1.2	4.2±1.5	-2.8±1.4	-1.4±1.7	NR	NR	NR
Roos-Jansåker et al, 2007 [22]							
Group 1: bone graft mixed with blood + resorbable membrane	1.52±1.16	2.86±2.00	-1.28±1.51	-1.59±2.0	NR	NR	NR
Group 2: bone graft alone	1.44±1.27	3.44±1.58	-1.61±1.61	-1.8±1.37	NR	NR	NR
P-value (difference between initial state and follow-up visits)	0.8	0.19	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	NR	-1.1 ± 2.1	18.1	NR	NR
Group 2: Bone graft (bovine mineral bone) + resorbable membrane	1.4 ± 1.04	2.4 ±1	NR	-2.4 ±1.3	-50	NR	NR
P-value (difference between the 2 groups)	0.251	0.084	NR	0.512	NR	NR	NR
Schwarz et al, 2015 [37]							
Case 1	3.25 ± 1.26	NR	NR	NR	NR	NR	NR
Case 2	3±1.41	NR	NR	NR	NR	NR	NR
Case 3 (*reinfection of mesial aspect)*	3.33±1.53	NR	NR	NR	NR	NR	NR
Case 4	3±1	NR	NR	NR	NR	NR	NR
Case 5 *(reinfection of mesial and distal aspects)*	1.0 ±1.41	NR	NR	NR	NR	NR	NR
Mean ± std. deviation *(excluding infected sites)*	3.52 ±0.88	NR	NR	NR	NR	NR	NR
Isehed et al, 2016 [25]							
EMD	0.9	2.8	NR	NR	NR	NR	NR
NO EMD	-0.1	3.00	NR	NR	NR	NR	NR
P-value	0.295	0.270	NR	NR	NR	NR	NR

Wiltfang et al, 2012 [38]							
Autogenous + xenogeneic bone graft Without membrane	3.5± 2.4	4.0± 1.8	-1.3± 0.4	NR	36	NR	NR
Roccuzzo et al, 2016 [29]							
Deproteinized mineral bovine bone + 10% collagen without membrane	NR	2.92 ±1.73	NR	NR	53.2 ±39.4	4.2±26.4	0.58±1.24
P-value	NR	<0.0001	NR	NR	<0.0001	0.15	0.001
Jepsen et al, 2016 [28]							
Test group: PTG + surgery conventional (mesial/distal)	3.61 / +3.56	2.8±1.3	NR	NR	NR	NR	NR
Control group: Conventional surgery alone (mesial/distal)	1.05 / +1.04	2.6±1.4	NR	NR	NR	NR	NR
P-value (statistical difference between groups)	<0.0001	NS	NR	NR	NR	NR	NR

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

- 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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