Long-term Radiographic and Clinical Outcomes of Regenerative Approach for Treating Peri-implantitis: A Systematic Review and Meta-analysis

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Purpose: *The purpose of this systematic review was to evaluate long-term outcomes of regenerative procedures for treating peri-implantitis.* ***Materials and Methods:*** *Electronic searches of five databases and hand searches of journals were performed to identify human trials that had treated more than 10 peri-implantitis lesions using a regenerative approach with a follow-up period of at least 36 months. To meet the inclusion criteria, studies had to report at least one of the following parameters: radiographic bone fill (RBF), probing depth (PD) reduction, clinical attachment level gain, bleeding on probing reduction, and mucosal level gain. The pooled weighted mean and the 95% confidence interval (CI) of each variable were estimated.* ***Results:*** *The searches yielded 1,412 records, and after evaluating titles, abstracts, and full texts, 5 case series and 1 controlled trial were included for quantitative data synthesis. Meta-analysis of the studies for the amount of RBF revealed a weighted mean of 2.41 mm (range, 1.46 to 3.30 mm) with 95% CI. For PD reduction, the weighted mean was 3.06 mm (range, 1.24 to 5.21 mm).* ***Conclusion:*** *There is limited evidence in the literature reporting long-term results of the regenerative approach for treating peri-implantitis. Within the limits of this meta-analysis, regenerative treatment of peri-implantitis resulted in a mean radiographic defect fill of 2.41 mm after a minimum healing time of 36 months. However, this finding must be interpreted with caution, since it is difficult to discern between grafting material and newly formed bone.* Int J Oral Maxillofac Implants 2016;31:1303–1310. doi: 10.11607/jomi.4691

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Peri-implant mucositis is an inflammatory condition of the soft tissues surrounding dental implants with no signs of bone loss following initial bone remodeling.[1] If not properly managed, this condition may progress into peri-implantitis, which includes both soft tissue inflammation and progressive loss of supporting bone.[1] Peri-implantitis is diagnosed when there is bleeding on probing (BOP) in addition to radiographic evidence of loss of supporting bone beyond marginal bone remodeling following implant insertion and crown placement. Additionally, clinical findings such as suppuration, deep probing depths ([PD] > 5 mm) or mucosal recession (MR) are often observed.[2,3] Recent studies have determined that peri-implantitis affects 2.7% to 47.1% of all implants.[4–8]

The primary goals of treating peri-implantitis are to resolve the inflammation and/or infection, halt the progression of disease, regenerate lost peri-implant surrounding tissues, and to achieve re-osseointegration on implant surfaces. While mechanical nonsurgical therapy may be an effective approach for treating peri-implant

mucositis,[9,10] surgical methods with adjunctive use of anti-infective agents are commonly applied for treating peri-implantitis.[9] These procedures include open-flap debridement in conjunction with anti-infective agents, resective approach for suprabony or shallow intrabony defects, and regenerative procedures for deep circumferential-type defects.[11]

Regenerative procedures using bone-replacement grafts with or without barrier membranes have been employed to resolve peri-implantitis.[12] Given the different decontamination methods,[13] grafting materials, and barrier membranes available, as well as the variety of surgical techniques, it has been difficult—if not impossible—to draw conclusions about the effectiveness of these methods and to determine the superiority of a specific approach.[14] Removing dental implants diagnosed with peri-implantitis may cause morbidity and may require more time and cost in terms of restoring the explanted site for possible placement of a new implant than would repair or regenerative procedures.[15] Nevertheless, the treatment outcomes following regenerative procedures for treating peri-implantitis should remain stable for a long time to justify the cost benefit of these procedures. Therefore, this study was conducted to evaluate long-term outcomes of regenerative approaches for treating peri-implantitis.

MATERIALS AND METHODS

Focused Question

How do the effects of regenerative treatment of peri-implantitis compare to those of other treatment modalities, such as open-flap debridement, after a minimum healing time of 36 months in human subjects?

Inclusion Criteria

Studies included in this review were human clinical trials published in English that had treated ≥ 10 implants with ≥ 36 months follow-up and had reported at least one clinical or radiographic parameter for evaluation of the efficacy of regenerative therapies in treating peri-implantitis. Screw-shaped implants with either smooth or rough surfaces were included. Clinical and radiographic parameters of interest were radiographic bone fill (RBF), PD reduction, clinical attachment level (CAL) gain, BOP reduction, and mucosal level (ML) gain.

Search Strategy

A search of four electronic databases—Ovid MEDLINE, PubMed, EMBASE, and Dentistry and Oral Sciences Source—for relevant studies published in English from January 1990 to April 2014 was performed. The search terms used, in which "mh" represented the MeSH terms and "tiab" represented the title and/or abstract, included the following: ("peri-implantitis"[mh] OR "peri-implantitis"[tiab] OR (("dental implantation, endosseous"[mh] OR "dental implants"[mh]) AND ("peri implant"[tiab] OR "peri-implantitis"[tiab]))) AND ("treatment"[tiab] OR "therapy"[tiab] OR "therapeutics"[tiab] OR "surgery"[tiab] OR "surgical"[tiab] OR "regeneration"[tiab] OR "regenerative"[tiab] OR "guided tissue regeneration"[mh] OR "bone graft"[tiab] OR "bone grafts"[tiab] OR "bone substitute"[tiab] OR "bone substitutes"[tiab]).

Additionally, a hand search was performed in dental and implant-related journals from January 2001 to April 2014, including the following: *Journal of Dental Research*; *Clinical Implant Dentistry and Related Research; Journal of Clinical Periodontology; Clinical Oral Implants Research; Journal of Periodontology; International Journal of Oral and Maxillofacial Surgery; International Journal of Oral & Maxillofacial Implants; Implant Dentistry; Journal of Prosthetic Dentistry; International Journal of Prosthodontics; Journal of Oral Implantology; Journal of Oral and Maxillofacial Surgery*; and *International Journal of Periodontics & Restorative Dentistry*, as well as *European Journal of Oral Implantology* from March 2008 to April 2014. In addition, a search of the references of included papers was conducted for publications that were not electronically identified. One examiner (VK) performed all the searches. Two reviewers (FS and VK) examined the full text of potential articles, and the articles' eligibility for this review was confirmed after discussion. The level of agreement between the reviewers regarding study inclusion was calculated using κ statistics. The screening process is shown in Fig 1.

Data Extraction

Two reviewers (FS and VK) reviewed the papers that met the inclusion criteria and extracted and processed data for analysis. Characteristics of the included studies and a summary of their reconstructive outcomes were extracted. If indicated, authors of the potentially qualified papers were contacted to obtain more detailed data.

Study Quality

The PRISMA (Preferred Reported Items for Systematic Reviews and Meta-Analysis) statement was followed to ensure proper methodology. For nonrandomized controlled clinical trials, the Newcastle-Ottawa Scale (NOS) was used to assess the quality of the studies.[16] The fact that some studies came from the same group could lead to some risk of bias due to data overlap; however, this meta-analysis verified that neither the number of patients nor the numerical results coincided in the studies.[17,18] For randomized clinical trials, the Cochrane Collaboration tool was applied to examine the potential risk of bias.[19]

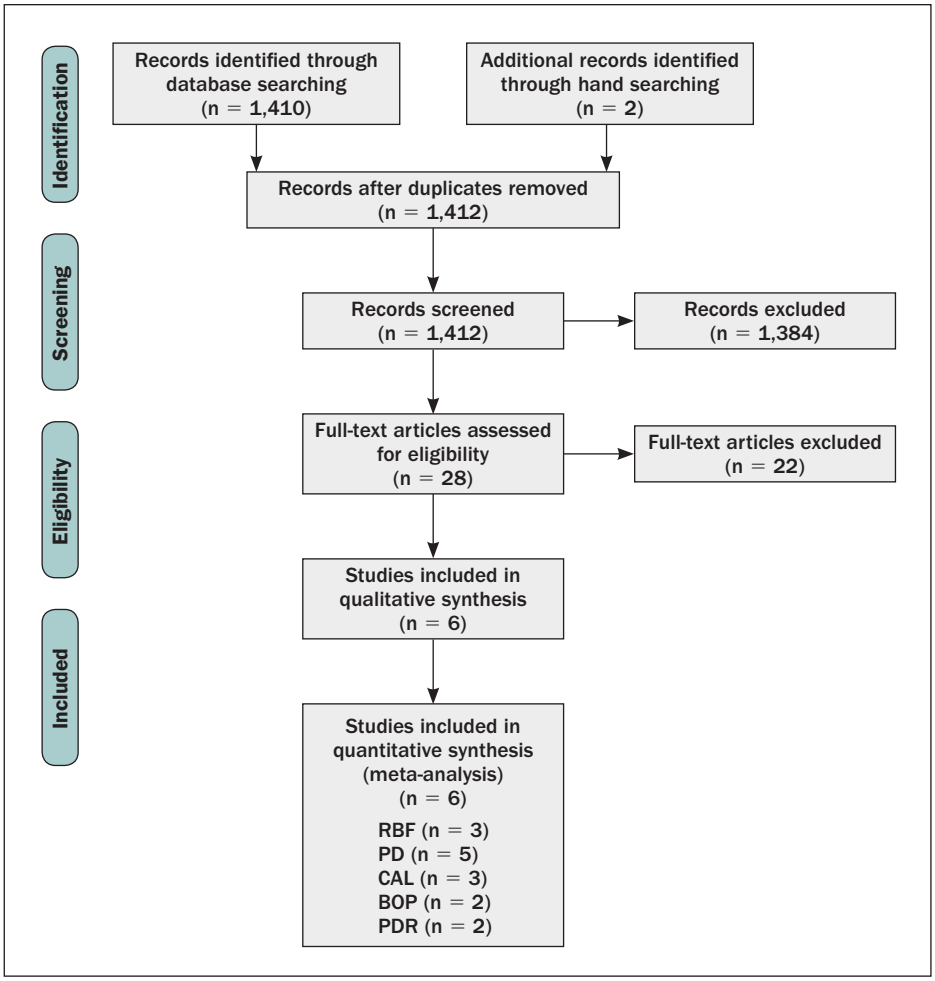

Fig 1 Flowchart illustrating the study selection for quantitative data synthesis. RBF = radiographic bone fill; PD = probing depth; CAL = clinical attachment level; BOP = bleeding on probing; PDR = probing depth reduction.

Data Analyses

The primary outcome was radiographic bone fill (RBF) and the secondary outcomes were changes of recorded peri-implant parameters. The pooled weighted mean (WM) and the 95% confidence interval (CI) of each variable were estimated using a computer program (Comprehensive Meta-analysis Version 2, Biostat). Random effects meta-analyses of the selected studies were applied to identify any bias caused by methodological differences among the studies. Forest plots were produced to graphically represent WM and 95% CI of the primary and secondary outcomes for all included studies, using the number of dental implants investigated as the analysis unit. In studies with more than one treatment arm, the arms were combined for statistical analysis. In addition, heterogeneity among the studies was assessed with the chi-square test; a *P* value less than .05 represents significant heterogeneity.

RESULTS

Study Selection and Data Extraction

The experimental flowchart is shown in Fig 1. The search initially retrieved 1,410 total citations. Two additional studies were retrieved through cross-referencing. After the titles and abstracts were reviewed, 28 articles were selected for full-text evaluation. Six articles qualified for final quantitative data synthesis. Features of the included studies and a summary of the outcomes for meta-analysis are presented in Tables 1 and 2.

Qualitative Assessment

The NOS was applied for nonrandomized clinical trials,[15,17,20–22] and moderate to low risk of bias (6.4 ± 0.6) was identified. In addition, the Cochrane Collaboration tool identified the only RCT included[18] as having a low

Table 1 Characteristics of Included Studies

Authors (year)	Study design	Follow-up period (mo)	Patient features		
			N	Age	Smokers (%)
Khoury and Buchmann[21] (2001)	CS	36	7 11 7	49.4 ± 5.2 55.5 ± 14.1 48.6 ± 8.1	ND
Deppe et al[22] (2007)[a]	CS	63	7 9	ND	ND
Schwarz et al[17] (2009)	CS	48	9 11	54.4 ± 12.5	0
Roos-Jansåker et al[20] (2011)	CS	36	15 17	65.6 ± 7.4 66.3 ± 6.7	68.4 70.6
Froum et al[15] (2012)	CS	49	15 23	58	ND
Schwarz et al[18] (2013)	RCT	48	12 9	62.2 ± 0.0	ND

[a]Control arms not listed in table because they are not reconstructive procedures. ND = not determined or reported; CS = case series; CHX = chlorhexidine; CA = citric acid (pH = 1); AA = air abrasive; PC = plastic curette; GC = graphite curette; Tn = tetracycline; PCC = phytogenic carbonate calcium; All = allograft; AP = alloplast; Resorb = resorbable membrane; SCTG = subepithelial connective tissue graft.

Table 2 Summary of the Regenerative Outcomes of the Evaluated Studies

Authors/Year	Radiographic outcomes		Other clinical					
	Initial bone loss	Bone fill (mm)	PI reduction	Initial PD (mm)	PD reduction (mm)	Initial CAL	CAL gain (mm)	Initial BOP (%)
Khoury and Buchmann[21] (2001)	3.5 ± 3.4 5.1 ± 3.1 6.4 ± 3.2	2.4 ± 2.7 2.8 ± 3.1 1.9 ± 3.2	ND ND ND	8.0 ± 0.5 8.2 ± 1.0 7.7 ± 0.5	5.1 ± 2.7 5.4 ± 3.0 2.6 ± 1.6	ND ND ND	ND ND ND	ND ND ND
Deppe et al[22] (2007)	6.8 ± 1.2 6.7 ± 1.5	ND ND	ND ND	4.8 ± 1.4 5.0 ± 1.3	2.3 ± 0.5 2.5 ± 0.5	5.9 ± 1.1 6.3 ± 1.3	2.1 ± 0.4 2.7 ± 0.5	ND ND
Schwarz et al[17] (2009)	ND ND	ND ND	(–) 0.5 ± 0.5 (–) 0.2 ± 0.6	6.9 ± 0.6 7.1 ± 0.7	1.1 ± 0.3 2.5 ± 0.9	7.3 ± 0.8 7.5 ± 0.9	0.6 ± 0.5 2.0 ± 1.0	80 79
Roos-Jansåker et al[20] (2011)	ND ND	1.3 ± 1.3 1.6 ± 1.2	ND ND	ND ND	ND ND	ND ND	ND ND	ND ND
Froum et al[15] (2012)	ND ND	3.8 ± 1.5 3.0 ± 0.8	ND ND	8.8 ± 1.9 7.9 ± 1.8	5.4 ± 1.5 5.1 ± 1.9	ND ND	ND ND	ND ND
Schwarz et al[18](2013)	ND ND	ND ND	0.0 ± 1.1 0.4 ± 0.7	5.5 ± 1.7 5.1 ± 1.5	1.2 ± 1.9 1.3 ± 1.8	6.7 ± 1.8 7.3 ± 1.9	1.5 ± 2.0 1.2 ± 2.0	100.0 95.2

ND = not determined or reported; PI = peri-implantitis; PD = probing depth; CAL = clinical attachment level; BOP = bleeding on probing.

risk of bias. Hence, plausible bias is unlikely to seriously alter the results.

Results of the Primary Outcome (RBF)

Of the included studies, two quasi-experimental studies[20,21] and one case series[15] provided data on RBF and thus could be meta-analyzed. The WM of bone fill was 2.41 mm (range, 1.46 to 3.30 mm), with a 95% CI of 1.04 to 3.79 mm (Fig 2). The *P* value for the chi-square test was .55, representing low heterogeneity among the studies.

Results of the Secondary Outcomes

The statistical results from each of the selected studies were converted into effect sizes and combined in the meta-analyses. The changes to the four peri-implant variables (PD, CAL, BOP, and ML) between baseline and the last follow-up were recorded and analyzed. The results and forest plots of meta-analyses for each clinical variable are demonstrated in Figs 3 to 5 and Supplemental Figs S1 to S3 (online only; go to www.quintpub.com/journals/omi).

Implant features					Surgical intervention			
N at BL	N at FE	Location	Body surface	Platform surface	Decontamination method	Grafting material	Membrane	Submerge
12 20 9	12 20 9	ND	R	S	CHX (0.2%) + CA + H_2O_2 + NaCl	Auto	N e-PTFE Resorb	Y
15	11	ND	ND	ND	AA	Auto + ß-TCP	e-PTFE	Y
17	13	ND	ND	ND	AA + CO_2 laser			
9 11	9 10	ND	ND	ND	PC + NaCl	AP XG	N Resorb	N
29 36	27 29	ND ND	R (1)/ S (26) R (1)/ S (28)	S S	H_2O_2 (3%) + NaCl H_2O_2 (3%) + NaCl	PCC PCC	N Resorb	N
19 32	19 32	ND	R	ND	GC + AA + NaCl + Tn + AA + CHX + NaCl + EMD + PDGF	XG or All	Resorb or SCTG	N
16 16	12 9	ND	R (10)/ S (1)/ ND (1) R (4)/ S (4)/ ND (1)	ND	IP + PC + NaCl IP + Er: YAG	XG	Resorb	N

RCT = randomized controlled trial; BL = baseline; FE = final examination; max = maxilla; mand = mandible; R = rough; S = smooth; EMD = enamel matrix derivatives; PDGF = platelet-derived growth factor; IP = implantoplasty; Auto = autogenous; XG = xenograft;

outcomes		
BOP Reduction (%)	Mucosal level gain (mm)	Complications
ND ND ND	ND ND ND	None 60% of implants (4 dehiscences, 5 membrane exposures, 1 fistula, 1 sequester formation) 56% of implants (2 dehiscences, 1 membrane exposure, 2 sequester formations)
ND ND	0.2 ± 0.6 (–) 0.2 ± 0.6	Severe infection in 1 patient, resulting in loss of 4 implants Grafts and 4 implants in 1 patient were lost after 10 months
34 51	0.4 ± 0.5 0.5 ± 0.4	Uneventful
ND	ND	Uneventful
ND	ND	87.6% membrane exposure
ND ND	ND ND	ND
85.2 71.6	0.3 ± 0.9 0.1 ± 0.3	Uneventful

Probing Depth Reduction. Five studies[15,17,18,21,22] were included for evaluating the amount of PD reduction. The WM was 3.06 mm (range, 1.24 to 5.21 mm), with a 95% CI of 1.78 to 4.35 mm (Fig 3). The P value for chi-square test was .21, indicating low to moderate heterogeneity among the studies. For investigating the percentage of PD reduction, the WM was 45.6% (range, 23.3% to 58.2%), with a 95% CI of 30.5% to 61.4% (Fig S2) and a P value for chi-square test of .34.

Clinical Attachment Level Gain. Three studies[17,18,22] were included for evaluating the amount of CAL gain. The WM was 1.76 mm (range, 1.34 to 2.43 mm), with a 95% CI of 0.90 to 2.62 mm (Fig 4) and a *P* value for chi-square test of .50. For investigating the percentage of CAL gain, the WM was 26.4% (range, 17.9% to 39.5%), with a 95% CI of 14.7% to 42.8% (Fig S2) and a *P* value for chi-square test of .39.

Bleeding on Probing. Two studies[17,18] were selected for evaluating the percentage of BOP reduction. The WM was 62.5% (range, 43.0% to 79.4%), with a 95% CI of 25.2% to 89.2% (Fig 5) and a *P* value for chi-square test of .32.

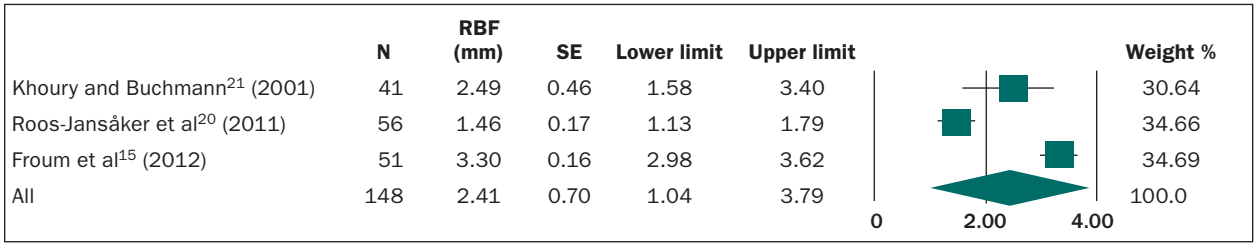

Fig 2 Meta-analysis for the amount of radiographic bone fill (RBF) among selected studies.

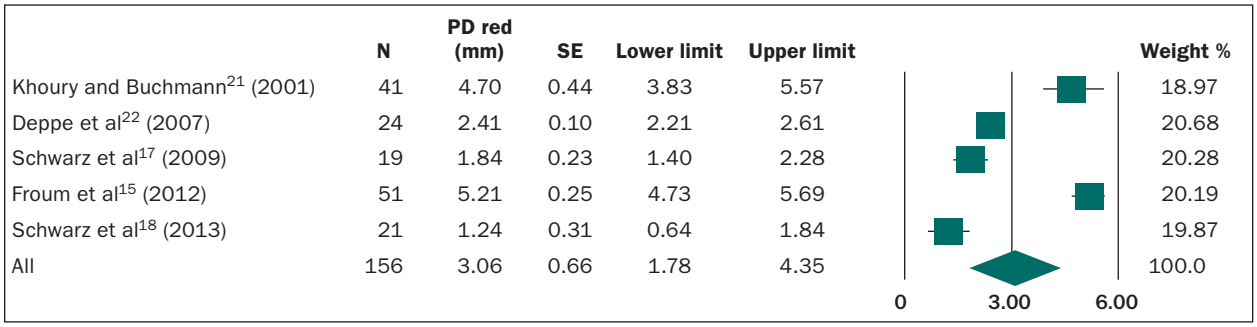

Fig 3 Meta-analysis for the amount of probing depth (PD) reduction among selected studies.

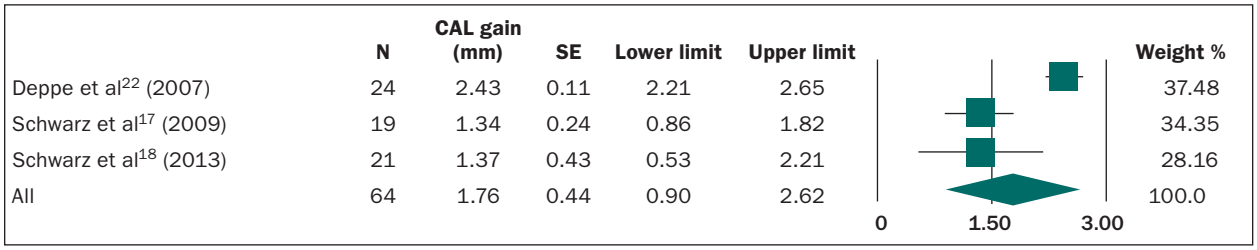

Fig 4 Meta-analysis for the amount of clinical attachment level (CAL) gain among selected studies.

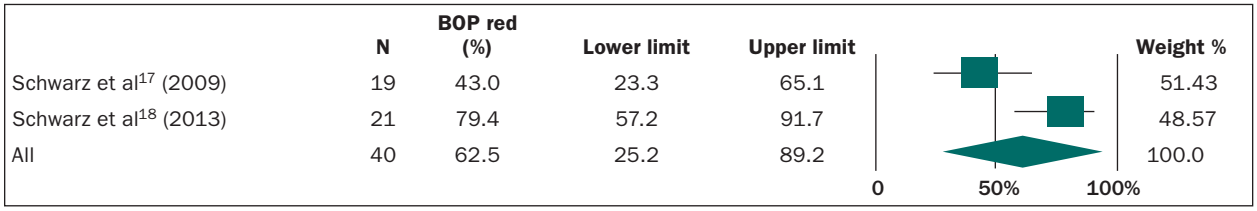

Fig 5 Meta-analysis for bleeding on probing (BOP) reduction (%) among selected studies.

Mucosal Level Gain. For ML gain, three studies[17,18,22] had data regarding ML change and presented a WM of 0.22 mm (range, –0.02 mm to 0.45 mm), with a 95% CI of –0.07 to 0.51 mm (Fig S3) and a *P* value for chi-square test of .42.

DISCUSSION

The focused question remains unanswered due to the lack of any controlled trial that compared regenerative treatment of peri-implantitis with other treatment modalities after a minimum follow-up period of 36 months. A weighted mean of 2.41 mm (range, 1.46 to 3.30 mm) was calculated for RBF after an observation period of at least 36 months. Caution should be exercised when interpreting these results, since only three studies[15,20,21] were included in this appraisal. Additionally, a tendency toward a positive outcome is expected mainly because of the significant amount of RBF reported in one of the studies.[15] It should be noted that the slow resorption rate and radiopaque nature of anorganic bovine bone could potentially influence the reported results of the aforementioned study. Neither of the other two studies reporting defect fill used xenograft particles.

Although the included studies reported various degrees of success in terms of filling the osseous defects

accompanied by other clinical outcomes, they did not address disease resolution—the main goal of treatment.[23] Only two studies[17,18,24] reported the percentage of BOP reduction—as 43% and 79%, respectively. Ideally, resolution of disease would mean an absence of clinical inflammation (eg, BOP) that indicates peri-implant health status[25]; however, most of the included studies did not evaluate change in BOP. It is also likely that known risk indicators for peri-implantitis, such as smoking, uncontrolled diabetes, and untreated periodontal disease,[2,26,27] have an unfavorable effect on treatment outcomes. Unfortunately, the information regarding these parameters was missing from most of the included studies.

Treating periodontal intrabony defects with bone grafting particles in combination with barrier membranes has been shown to result in more CAL gain and PD reduction compared with bone substitutes alone.[28,29] It has been stated that adding a cell-occlusive membrane with the use of a bone graft may be beneficial for specific osseous defects around implants.[11] However, two of the included studies[15,16] demonstrated that placing a membrane over the bone substitute did not improve long-term results, and after 36 months of follow-up there was no statistically significant difference in the amount of bone fill between the two groups. Thus, the clinical benefits of using a membrane in combination with bone grafting material for the treatment of intrabony peri-implantitis lesions are disputable and seem to be of little clinical value. The high exposure rate (87.6%)[16] of the membranes during the healing period may justify the unfavorable results. This finding has also been confirmed in experimental studies.[30–32]

Agreements and Disagreements with Previous Studies and Reviews

Findings of the present review in terms of calculated weighted mean for RBF are in accordance with previous reviews, which reported a weighted mean of 2.17 mm of RBF after at least 1 year of follow-up[33] and 2.16 and 2.10 mm of RBF[33,34] after 6 months of follow-up with and without using barrier membranes, respectively. In the latter,[34] 0.06 mm more bone fill was reported with the use of cell-occlusive membranes, thus showing limited clinical value.

Implications for Clinical Practice

Taking the data of this review and previous reports[33,34] into consideration, it can be assumed that attempts for reconstruction of peri-implantitis lesions may result in about 2 mm of defect fill, which demonstrates the limited efficacy of this approach. However, in early stages of peri-implantitis in esthetic areas, a regenerative approach combined with excellent mechanical debridement and anti-infective therapy may be attempted.

Implications for Research

In the current literature there is a lack of well-designed controlled studies with large sample sizes. Outcomes of the treatment need to be assessed at a multivariable level to identify the sources of heterogeneity. Clinical trials that focus on patient/implant-centered outcomes and disease resolution should be continued. Additionally, potential sources of bias should be reported for quality assessment purposes. The clinical efficacy of different grafting materials deserves additional investigation.

Limitations

Some limitations of the present review must be addressed. It was not possible to analyze all data for an individual patient pool because the included studies did not uniformly report all of the outcomes. Another important issue is the patient population treated. Individual patient factors, such as the presence of diabetes or other comorbidities, are of importance in clinical practice. The same is true for smoking habits; data regarding the smoking habits of patients were missing in four of the studies,[15,17,21,22] and in one study[20] the majority of the patients were smokers. Another limitation is that the literature search was confined to papers published in English, which may introduce a selection bias. Additionally, the included studies were mostly case series with inconsistent methodologies and different definitions of peri-implantitis, some of which represent lower levels of evidence. The validity of the only controlled trial[18] included in the analysis is also questionable, as the trial lost more than 20% of its baseline subjects for follow-up.[35] Moreover, the small number of selected studies could potentially bias results, and readers should interpret the results with caution.

CONCLUSIONS

Based on the results from three available studies, regenerative procedures for management of peri-implantitis resulted in a mean RBF of 2.41 mm after a minimum period of 36 months of observation, accompanied by improvement of other clinical parameters. Systemic conditions of the subjects, morphology of the defects, methods for decontamination, and types of bone grafting materials used are possible factors that may have influenced the outcomes. Although there are some encouraging findings, limited long-term data are available on the stability of regenerative approaches for treating peri-implantitis. The authors conclude that regenerative procedures are among

several options—including nonsurgical, chemotherapeutic, resective, or implant removal—that may be considered for dealing with peri-implantitis.

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