Received: 2 May 2023 | Revised: 28 June 2023 | Accepted: 21 August 2023

DOI: 10.1111/prd.12523

Periodontology 2000 WILEY

REVIEW ARTICLE

Selecting biomaterials in the reconstructive therapy of peri-implantitis

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1 | INTRODUCTION

Peri-implantitis is a plaque-mediated inflammatory condition characterized by progressive bone loss. In fact, local predisposing, precipitating, and acceleratory factors were demonstrated to be key in understanding the site-specific prevalence of this disorder.[1] This entity jeopardizes the longevity of dental implants, thus negatively impacting the quality of life of patients. Moreover, peri-implantitis is suggested to lead to an increased systemic status of inflammation.[2,3] This may increase an individual's susceptibility to life-threatening conditions.[2] Therefore, peri-implant infections must be promptly diagnosed and eliminated.

Several options are recommended to relieve the inflammation and remove the infection. Accordingly, implant removal or therapeutic maneuvers to establish a healthy ecosystem in the peri-implant environment have been suggested.[4] While the former has been proven to be more predictable, the latter has been shown to be more conservative. Indeed, implant removal is commonly associated with regenerative procedures of the alveolar bone deformity that often demand time and are more costly.[5] Disease severity, implant expendability for biomechanical reasons, or esthetic demand seem to be a few of the leading aspects in the decision-making process on maintaining or extracting implants showing peri-implant lesions.

Peri-implantitis is an inflammatory disorder and the primary endpoint in the management of this disorder is a condition of health characterized by shallow pockets with a dominant population of aerobic bacteria. The therapeutic modality relies primarily upon implant position, soft tissue characteristics, and defect configuration. Nonsurgical measures have been shown to be unsatisfactory in terms of disease resolution.[6] Hence, surgical strategies are often necessary. This therapeutic option demonstrated enhanced predictability and effectiveness levels in the long-term stability of the peri-implant hard and soft tissues.[7]

In general, peri-implantitis bone defects exhibiting contained defects are prone to show favorable reconstructive/regenerative outcomes together with a consistent reduction in the pocket depth.[8,9] On the other hand, noncontained defects are discouraged from applying the principles of bone regeneration by means of using bone substitutes and/or barrier membranes. Despite these indications, the benefit provided by biomaterials in the reconstructive management of peri-implantitis bone defects remains unclear. Therefore, the aim of this narrative review is to address major clinical concerns regarding the effectiveness and plausibility of using biomaterials in peri-implantitis therapy.

2 | CRITERIA TO SUCCEED IN PERI-IMPLANTITIS THERAPY

The objective in the management of peri-implantitis is to create an environment that is manageable by both the patient and the clinician. This is achieved by reducing the probing pocket depth (PPD)

to ≤5 mm. As a result, bleeding on probing (BOP) and suppuration (SUP) are conditioned to be dropped/eliminated. Furthermore, progressive bone loss should be arrested when inflammation is resolved. Regardless of the type of surgical intervention, even in reconstructive procedures, the primary endpoint for disease management is to reduce the PPD. In fact, in reconstructive procedures, the goal is to reduce the PPD by augmenting peri-implant bone support. Moreover, patient satisfaction must also be incorporated within the success criteria. In this sense, mucosal recession (MR) occurs as part of the resolution of inflammation.[10] Therefore, concerns related to aesthetics must be underlined when delivering the treatment plan, as it may interfere with patient satisfaction.

3 | LIMITATIONS IN PERI-IMPLANTITIS THERAPY

The dominant factors that dictate a hopeless prognosis and where, therefore, implant removal is indicated are the following:

- A patient's unwillingness to enroll in a professionally administered maintenance program and inadequate motivation to perform self-performed oral hygiene measures for plaque control. Lack of supportive care was demonstrated to be one indicator of therapeutic failure (OR = 5).[11]
- Implants exhibiting advanced peri-implant bone loss. Studies have demonstrated a significantly lower likelihood of success in the surgical management of peri-implantitis if the lesions extend ≥50% of the implant length.[11,12] In fact, baseline advanced bone loss is linked to therapeutic failure (OR = 20).[13]
- Impossibility of addressing local factors associated with the onset of disease.[14] Identifying and modifying local predisposing factors is key in preventing recurrence. Among them, three major factors are to be considered: soft tissue characteristics, prosthesis design, or implant position in a three-dimensional perspective.[14]
- Impossibility to decontaminate the implant surface due to characteristics related to defect configuration or to the armamentarium available by the operator. A broad variety of strategies have been used for implant surface decontamination. Mechanical methods have been demonstrated to be effective in eliminating calculus deposits and residual debris; however, the presence of undercuts and the grooves and porosities along the implant surface make it difficult to achieve an aseptic surface. Hence, in conjunction with mechanical methods, the use of chemical adjuncts has been suggested to dilute bacterial concentrations and to eliminate endotoxins. Moreover, pharmacological adjuncts have also been recommended to diminish the bacterial load. Other strategies, such as use of lasers, implantoplasty (in particular for areas outside the reparative potential/bony envelope) and electrolysis, have been advised for implant surface decontamination to promote peri-implant health.[15]
- Expendable implants due to their inadvertent biomechanical, functional, or esthetic role can be removed regardless of the extent of the disease.
- Implants exhibiting peri-implantitis in the anterior maxillary area and demand esthetic outcomes. In general, implants presenting moderate or advanced peri-implantitis lesions and/or with a lack of interproximal support and/or implants in an inadequate position that lead to deficient restorations have a more unfavorable prognosis.[16]

On the other hand, patient's willingness and commitment to manage the disorder is important to be assessed. In this sense, the sequelae led by implant removal and the added outlay associated with implant-site development interventions and prosthesis rehabilitation must be thoroughly communicated.

4 | INDICATIONS FOR RECONSTRUCTIVE THERAPY

In general, contained defects are prone to show favorable reconstructive outcomes when managed by means of regeneration.[8] Schwarz et al.[8] tested the effectiveness of reconstructive therapy by means of anorganic bovine bone and collagen membrane in three different scenarios, including buccal dehiscence + semi-circumferential defects, buccal dehiscence + circumferential defects, or pure circumferential intrabony defects. At the 6-month follow-up, significant differences were noted in the PPD (mean difference approximately 1 mm) and clinical attachment level (mean difference approximately 1 mm), favoring the defects exhibiting a pure circumferential configuration. Similarly, Aghazadeh et al.[9] explored the influence of defect features on reconstructive outcomes when regeneration was applied by means of autologous or xenogeneic bone. Circumferential and deeper defects showed more defect fill at the 12-month follow-up than partially contained defects (2-3-wall defects). Monje et al.[17] further showed the positive association between baseline defect angle and radiographic bone gain. In fact, defect angles <40° are more prone to show predictable and favorable reconstructive outcomes (radiographic bone gain). These findings are thus aligned with the existing evidence in periodontal tissue regeneration.[18,19] Therefore, bone defects presenting adjacent bony peaks that enhance support and continence to the bone graft are indicated for reconstructive therapy. Along these lines, it is fundamental to understand the existing limitations of reconstructive therapy concerning defect configuration (Figure 1). In combined defects, it was described that the area of the implants outside the reparative potential is not indicated for reconstruction but rather for resection.[20] Hence, in cases exhibiting areas above the apical-most adjacent bony peak or outside the

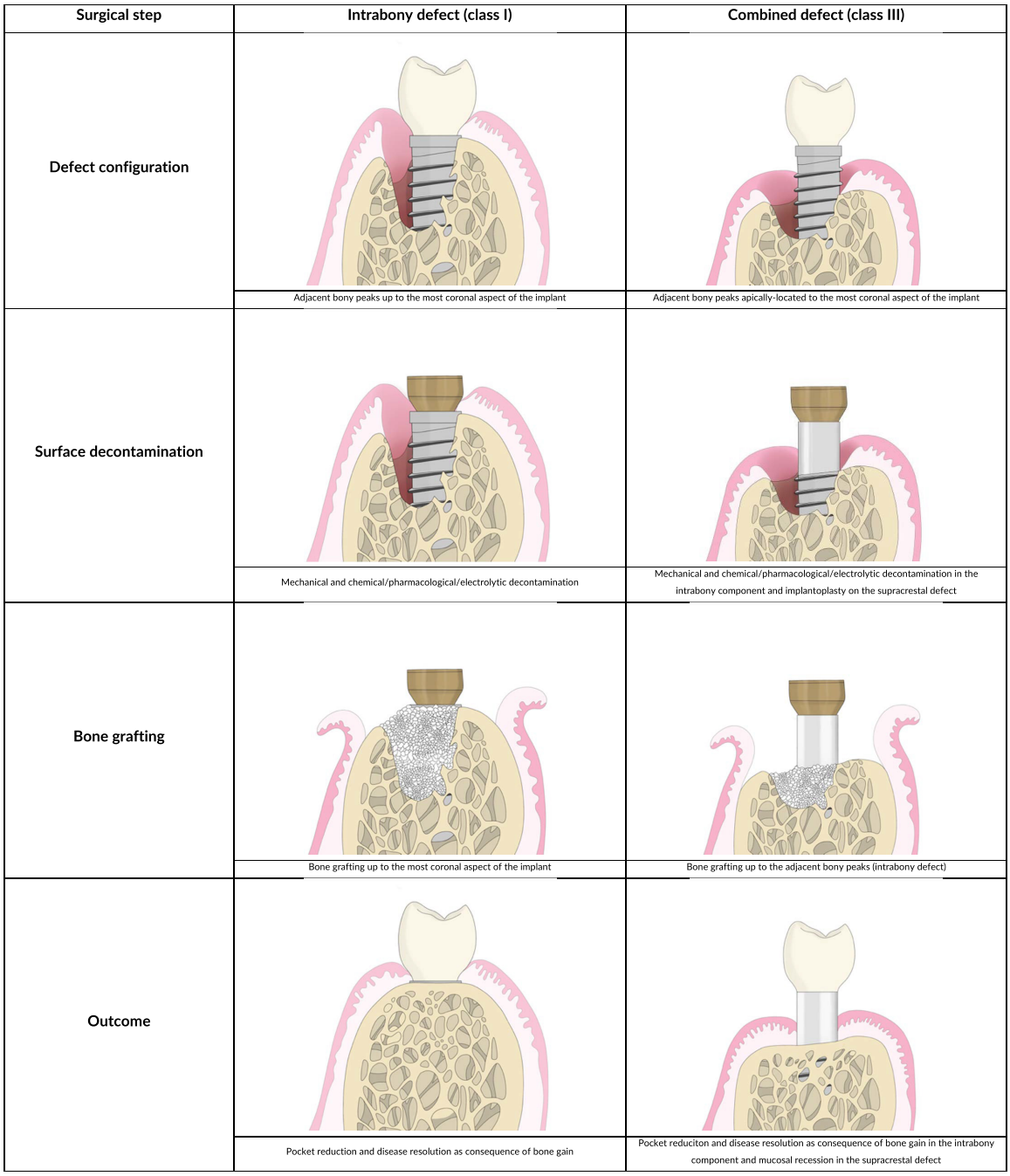


FIGURE 1 Reconstructive therapy is indicated in scenarios exhibiting intrabony compartments. On the left side, reconstructive therapy of a 3-wall defect where surface decontamination and bone regeneration are indicated to enhance the support while reducing the pocket depth. On the right side, a combined defect. A combined therapeutic modality including implantoplasty for the supra-crestal component is recommended to reduce pocket depth as a consequence of intentional mucosal recession in the supra-crestal component and bone gain in the intrabony compartment.

bony envelope, the reparative potential might be overestimated, which may lead to therapeutic failure. Accordingly, reconstructive therapy would be indicated in the following bone defect configurations (Tables 1 and 2):

- Class Ib: 2/3-wall defect where in case of implants positioned too buccally, only the area inside the alveolar envelope is aimed at being reconstructed.
- Class Ic: Circumferential defect (4-wall defect)
- Class IIIb: 2–3 walls defect + supra-crestal defect where in case of implants positioned too buccally, only the area inside the alveolar envelope and below the adjacent bony peak is aimed at being reconstructed.
- Class IIIc: Circumferential defect (4-wall defect)+supra-crestal defect where only the area below the adjacent bony peak is aimed at being reconstructed.

Moreover, it is known that regenerative therapy in smokers often leads to undesired outcomes due to the altered immunologic and angiogenic response that negatively impacts osteogenic activity. Thus, in smokers, particularly heavy smokers (≥10 cig/day), this intervention would not be indicated.

5 | EFFICACY OF RECONSTRUCTIVE THERAPY

Multiple clinical trials have validated this approach alone[21–23] or in combination with other measures, such as implantoplasty[24,25] combined with defects exhibiting supra-crestal components. It is worth stating that randomized clinical trials (RCTs) are sparse. Wohlfahrt et al.[26] tested the impact of bone grafting with titanium granules of intrabony defects ≥4 mm in depth by applying a submerged healing approach compared to open flap debridement (OFD) at 12 months. A significant effect of radiographic bone gain was demonstrated for the sites reconstructed, while clinical improvements were equal for both groups. The 7-year follow-up examination,[27] however, showed progressive bone loss for both groups, leading to therapeutic failure. Jepsen et al.[21] compared the use of titanium granules for reconstructive therapy and OFD in a multicenter 12-month follow-up study of 3-4-wall intrabony defects applying transmucosal healing. The reconstructive group outperformed in the radiographic bone fill; nonetheless, PPD and BOP reduction were similar, leading to an even disease resolution rate. Isehed et al.[28] compared enamel matrix derivatives (EMD) to OFD of angular peri-implant bone defects at the 60-month follow-up. It was shown that radiographic bone level was superior in sites managed by means of reconstructive therapy (mean difference approximately 1 mm). Nevertheless, no significant differences were noted in the evaluated clinical parameters. Renvert et al.[22] performed a 12-month RCT to assess the effect of reconstructing ≥3-wall defects with xenografts compared to OFD. The radiographic bone level was significantly higher in the test group. The BOP rate was significantly higher at the control sites. In fact, disease resolution was lower in the control group (5%) than in the test group (42%). Derks et al.[29] in a 12-month multicenter study tested the effect of grating by means of xenograft with 10% collagen of ≥3-4-wall defects following a transmucosal healing approach when

TABLE 1 Indications of defect configurations for reconstructive therapy and clinical recommendations.

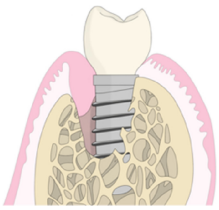
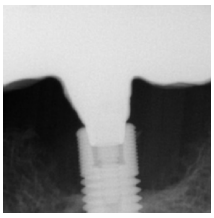
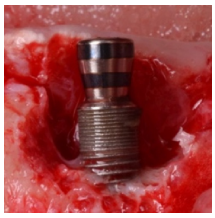
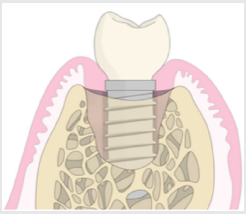
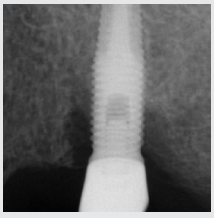
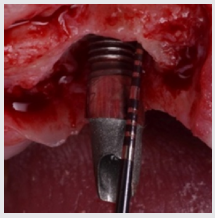
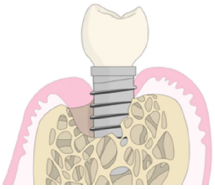
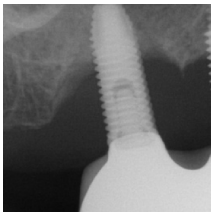
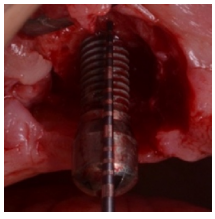
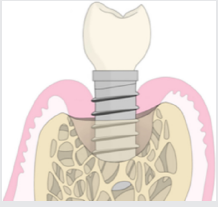
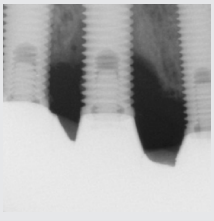
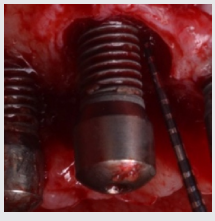
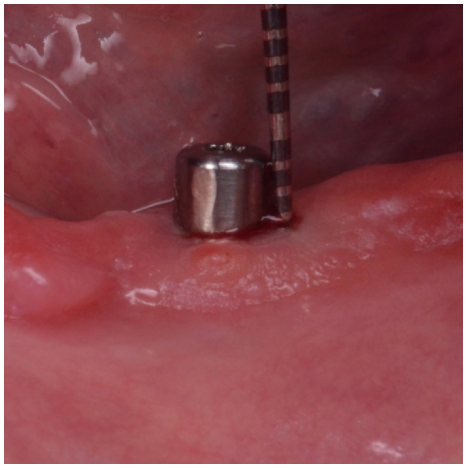
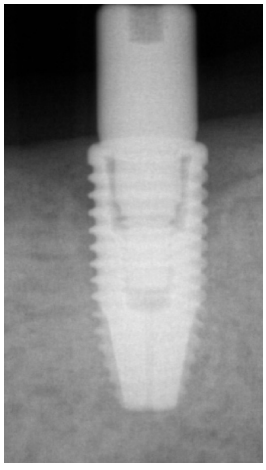
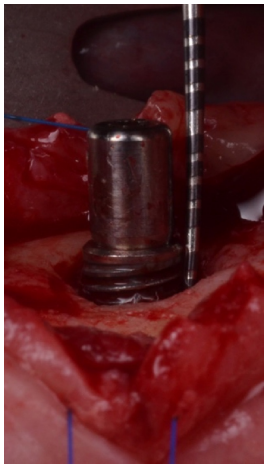
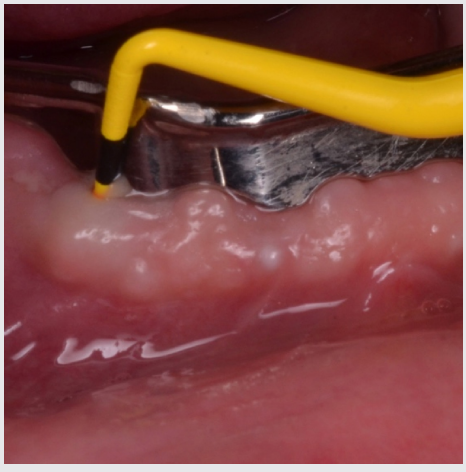
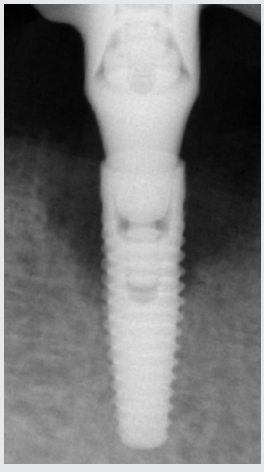
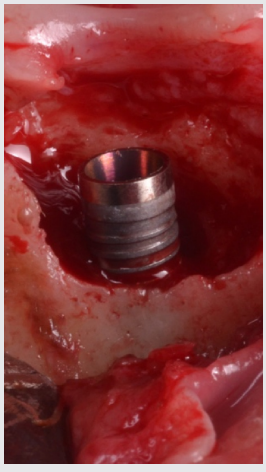
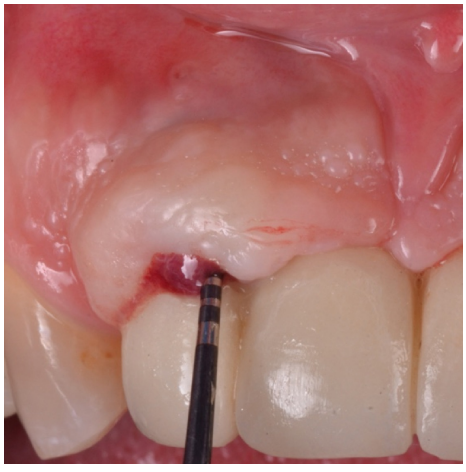
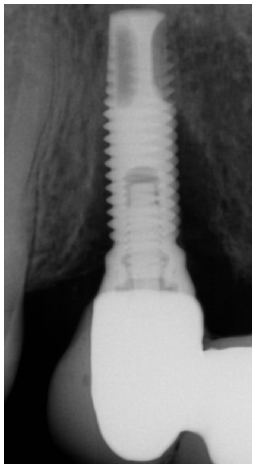
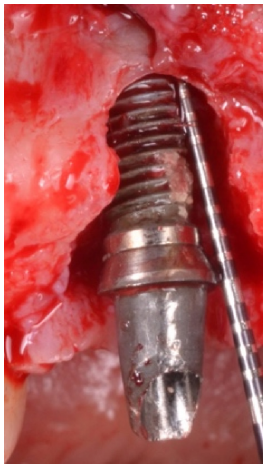
Defect configuration (Monje et al. 2019)	Illustration	Radiographic image	Intraoperative image	Clinical recommendation
Class Ib				Check bucco-lingual implant position to understand the reparative potential
Class Ic				Accommodate decontamination methods according to the defect entrance
Class IIIb				Evaluate the adjacent bony peaks and the bucco-lingual implant position to assess the reparative potential
Class IIIc				Evaluate the adjacent bony peaks to assess the reparative potential

TABLE 2 Severity of peri-implantitis bone defects.

Severity (Monje et al. 2019)	Clinical image	Radiographic image	Intraoperative image
Slight (MBL <25%)			
Moderate (MBL 25–50%)			
Advanced (MBL >50%)			

compared to OFD. It was demonstrated that reconstructive therapy did not offer benefit in terms of radiographic bone gain or clinical parameters but a significant reduction in MR.[29] Hence, in general, reconstructive therapy showed conflicting outcomes. The limited evidence together with the uneven methodologies concerning the reconstructive bone substitute and surface decontamination strategies preclude strong conclusions (Table 3).

6 | EFFECTIVENESS OF RECONSTRUCTIVE THERAPY

Understanding the paucity of data derived from RCTs, it is critical to further assess the effectiveness of reconstructive therapy demonstrated in cohort studies. Deppe et al.[30] analyzed the effect of grafting infra-osseous bone defects by means of tricalcium phosphate and

TABLE 3 Efficacy of surgical reconstructive therapy of peri-implantitis.

Author (year)	Study design	Follow-up (months)	N patients (total)	N patients/ group (sites)	Intervention	Defect configuration (number of walls)	Decontamination strategy	Healing protocol (submerged/ transmucosal)	Bone graft
Aghazadeh et al. (2022)[9]	RCT	72	39	16 (25) 23 (38)	Reconstructive therapy	2, 3 and circumferential	Ti curettes +3% Hydrogen peroxide + Saline	Transmucosal/ nonsubmerged	AB DBBM
Derks et al. (2022)[29]	MRCT	12	138	67 (68) 69 (69)	OFD Reconstructive therapy	Circumferential	Ti curettes + Ti brushes + Saline	Transmucosal/ nonsubmerged	– DBBMC
Hamzacebi et al. (2015)[57]	RCT	6	19	9 (19) 10 (19)	OFD Reconstructive therapy	2, 3, and circumferential	Ti brush + CA or Tetracycline HCL + Saline	Transmucosal/ nonsubmerged	– –
Isehed et al. (2018)[28]	RCT	72	29	14 (14) 15 (15)	OFD Reconstructive therapy	Angular defect (not specified)	US + Ti instruments + NaCl	Transmucosal/ nonsubmerged	– –
Jepsen et al. (2016)[21]	MRCT	12	63	30 (30) 33 (33)	OFD Reconstructive therapy	Circumferential	Ti brushes +3% Hydrogen peroxide + Saline	Transmucosal/ nonsubmerged	– PTGs
Polymeri et al. (2020)[74]	RCT	12	24	11 (11) 13 (13)	Reconstructive therapy	3	Ti curettes +3% Hydrogen peroxide + Saline	Transmucosal/ nonsubmerged	DBBM HA
Renvert et al. (2018)[75]	RCT	12	41	20 (20) 21 (21)	OFD Reconstructive therapy	3 and 4	Ti curettes +3% Hydrogen peroxide + Saline	Transmucosal/ nonsubmerged	– HA
Renvert et al. (2021)[22]	MRCT	12	66	32 (32) 34 (34)	OFD Reconstructive therapy	Circumferential (270°)	Ti brushes + Ti curettes +3% Hydrogen peroxide + Saline	Transmucosal/ nonsubmerged	– DBBM
Schwarz et al. (2006)[53]	CS	6	22	11 (11) 11(11)	Reconstructive therapy	Semi/or circumferential	Plastic curettes + Saline	Transmucosal/ nonsubmerged	HA DBBM
Wohlfahrt et al. (2012)[26]	RCT	12	32	16 (16) 16 (16)	OFD Reconstructive therapy	1,2 and 3	Ti curettes +24% EDTA gel + Saline	Submerged	– PTGs

Abbreviations: AB, autogenous bone graft; CS, case series; DBBM, deproteinized bovine bone mineral; DBBMC, deproteinized bovine bone mineral collagen, HA, hydroxyapatite/tricalcium phosphate; EMD, enamel matrix derivative protein; MRCT, multicenter randomized controlled clinical trial; OFD, open flap debridement; PRF, platelet-rich fibrin; PTGs, porous titanium granules; RCT, randomized controlled clinical trial; Ti, titanium.

nonresorbable barrier membranes after surface decontamination with a CO_2 laser or air-powder abrasive device in a 60-month follow-up study. The radiographic bone level was approximately 2 mm higher than the preoperative level. Likewise, Roos-Jansaker et al.[31] evaluated the effectiveness of grafting peri-implant bone defects with a nonbovine-derived bone substitute and a barrier membrane after decontaminating the surface with 3% hydrogen peroxide by applying a submerged approach in a 12-month study. PPD was significantly reduced by 4.2 mm, and a defect fill of 2.3 mm was reported. Similarly, Schwarz et al.[8] using a combination of anorganic bovine bone with a collagen membrane showed an average reduction of approximately 2.5 mm in PPD with a clinical bone fill/gain of approximately 2.5 mm, which varies according to the defect configuration. Wiltfang et al.[32] in a prospective 12-month follow-up case series demonstrated the effectiveness of reconstructive therapy using autogenous bone and a xenograft in an equal ratio after decontaminating the implant surface by means of etching gel. In fact, radiographic bone gain of 3.5 mm with an average reduction of PPD of 4 mm was shown. Mercado et al.[33]

Barrier membrane	Biologic	Antibiotics	Probing depth reduction (mm)	Bleeding score reduction (%)	Suppuration reduction (%)	Mucosal recession (mm)	Radiographic bone gain (mm)	Disease resolution (%)	Confounders of disease resolution
RCM	–	Azithromycin 250 mg 2/Day 5d	1.7	55.6	NR	NA	0.7 (–)	36.0	• Number of reinstrumentations during, follow-up period • Current smokers
–			2.8	50.6	NR		1.6	78.3	
–	–	Amoxicillin 750 mg 2/Day 10d	3.7	49.6	NR	1.1	1.1	13.5	• Severity of peri-implantitis of the included patients
–			3.7	44.8	NR	0.7	1.1	16.4	
–	–	Metronidazole 500 mg 3/Day 7d	2.0	44.0	NR	0.2 (–)	NA	NA	• Absence of demographic data analysis • Absence of radiographic analysis • No postoperative professional prophylaxis
–	PRF		2.8	54.0	NR	0.5	NA	NA	
–	–	–	NA	27.5	43	NA	1.3	NA	• Absence of periodontal records • Absence of demographic data analysis
–	EMD		NA	10	60	NA	1.4	NA	
–	–	Amoxicillin 500 mg 3/day and Metronidazole 400 mg 2/Day 8d	2.6	45.4	24.6	NA	1.0	23.0	• History of periodontitis • Current smokers • Implant brand • Time interval recalls
–			2.8	56.1	26.8		3.6	30.0	
–	–	Amoxicillin 500 mg 3/day and Metronidazole 500 mg 2/Day 8d	3.6	55.5	79.5	NA	2.5	18.0	• History of periodontitis
			3.7	50.0	84.6		3.0	0.0	
–	–	Azithromycin 500 mg 1 day and 250 mg 1/Day 2–4d	2.5	65.0	NR	0.2	0.2	5.0	• Peri-implant defect morphology • DM • Implant brand
–			3.6	52.4	NR	0.2	0.7	42.9	
–	–	Azithromycin 500 mg 1 day and 250 mg 1/Day 2–4d	2.3	1.0 (mBI)*	1.3 (±1.7)	0.9	1.1	NA	• History of periodontitis or active periodontitis • Implant brand
RCM			1.9	0.9 (mBI)*	1.5 (±1.3)	0.5	2.3	NA	
–	–	–	2.1	52.0	NR	0.3	NA	NA	• Absence of radiographic measurement analysis • Short follow-up
RCM			2.6	50.0	NR	0.3	NA	NA	
–	–	Amoxicillin 500 mg 3/day and Metronidazole 400 mg 2/Day 10d	2.0	56.0	NR	NA	14.8 (%)	NA	• Current smokers • History of periodontitis
–			1.7	38.0	NR	NA	57.0 (%)	NA	

reported the therapeutic outcome at the 36-month follow-up using EMD and inorganic bovine bone with 10% collagen. At the latest examination, it was noted that PPD reduction and radiographic bone gain amounted to ~5 and ~3 mm, respectively.[34] In a longitudinal study, Froum & Kim assessed the clinical and radiographic bone levels of advanced peri-implantitis defects managed by means of platelet-derived growth factor (PDGF) or EMD and a mixture of anorganic bovine bone and mineralized allograft. PPD was subjected to significant reduction (6.7 mm) and bone level gain (3.6 mm) at the latest follow-up. In terms of survival, La Monaca et al.[35] in a 60-month study showed a 100% survival rate, achieving 59% disease resolution. Interestingly, Roccuzzo et al.[36] in a 60-month study on 51 patients agreed on these findings. A relatively high implant survival rate of 80% was shown in patients who adhered to supportive maintenance care. Of these patients, 45% demonstrated disease resolution. Hence, based on existing cohort and case report studies, reconstructive therapy is suggested to be safe and effective in terms of PPD reduction, disease resolution, marginal bone level gain and implant survival (Table 4).

TABLE 4 Effectiveness of reconstructive therapy of peri-implantitis

Author (year)	Study design	Follow-up (months)	N patients (total)	N patients (sites)	Intervention	Defect configuration (number of walls)	Decontamination strategy	Healing protocol (submerged/transmucosal)	Bone graft
Astolfi et al. (2021)[76]	RCS	24 to 96	28	14 (16)	Reconstructive therapy + maintenance of the prosthesis	2 and 3	Mini-five curettes +3–5% Hydrogen peroxide +0.12% Chlorhexidine + Implantoplasty	Transmucosal/nonsubmerged	DBBM
				14 (16)	Reconstructive therapy + removal of the prosthesis				
de Tapia et al. (2019)[77]	RCT	12	30	15 (15)	Reconstructive therapy	2, 3 and 4	Plastic US +3% Hydrogen peroxide + Ti brush	Transmucosal/nonsubmerged	HA
				15 (15)			Plastic US +3% Hydrogen peroxide		
Froum et al. (2022)[34]	RCS	36 to 180	38	38 (46)	Reconstructive therapy	NR	Ti curettes + Ti brushes + Minocycline (50 mg/mL) + Saline + AP + CA	Transmucosal/nonsubmerged	FDBA + DBBM
La Monaca et al. (2018)[35]	PCS	60	34	34 (34)	Reconstructive therapy	NR	Ti curettes + US + Ti brush + AP + 3% Hydrogen peroxide +0.12% Chlorhexidine + Tetracycline hydrochloride + Saline	Transmucosal/nonsubmerged	FDBA
Mercado et al. (2018)[33]	PC	36	30	30 (30)	Reconstructive therapy + CTG (esthetic zone)	Circumferential	US +24% EDTA + Saline	Transmucosal/nonsubmerged	DBBMC + EMD + Doxycycline 100 mg
Monje et al. (2020)[49]	PCS	12	15	15 (27)	Reconstructive therapy	2 and 3	Mini-five and Gracey curettes + Implantoplasty +3% Hydrogen peroxide +0.12% Chlorhexidine	Submerged	DBBM + AB
Nart et al. (2018)[46]	PCS	12	13	13 (17)	Reconstructive therapy	2 and 3	Stainless steel curettes + Implantoplasty + US +3% Hydrogen peroxide + Saline	Transmucosal/nonsubmerged	50% vancomycin FDBA +50% tobramycin FDBA
Pilenza et al. (2022)[78]	RCS	12	11	11 (20)	Reconstructive therapy	NR	AP + 11 mg Povidone-iodine/ml	Transmucosal/nonsubmerged	HA + EMD
Roccuzzo et al. (2021)[36]	PCS	60	51	51 (51)	Reconstructive therapy	2, 3 and 4	Ti curettes + Ti brushes +24% EDTA +1% Chlorhexidine gel	Transmucosal/nonsubmerged	DBBMC
Roos-Jansåker et al. (2007)[31]	PCS	12	12	12 (16)	Reconstructive therapy	NR	Ti instruments +3% Hydrogen peroxide + Saline	Submerged	NBDBS
Schwarz et al. (2010)[8]	PCS	12	27	27 (27)	Reconstructive therapy	Semicircumferential (Class Ib)[b]	Carbon curettes + Saline	Transmucosal/nonsubmerged	DBBM
						Circumferential (Class Ic)[b]			
						Circumferential (Class Ie)[b]			
Wang et al. (2021)[79]	RCT	6	24	12 (12)	Reconstructive therapy	2, 3, and circumferential	Piezoelectric + Stainless steel scalers + Implantoplasty	Transmucosal/nonsubmerged	FDBA
				12 (12)			Piezoelectric + Stainless steel scalers + Er:YAG laser + Implantoplasty		

Barrier membrane	Biologic	Antibiotics	Probing depth reduction (mm)	Bleeding score reduction (%)	Suppuration reduction (%)	Mucosal recession (mm)	Radiographic bone gain (mm)	Disease resolution (%)	Confounders of disease resolution
RCM	—	Amoxicillin 875/125 mg + Metronidazole 250 mg 3/Day 7d	NR	70.0	95.0	NA	2.8	NR	• Absence of demographic data • No postoperative professional prophylaxis
			NR	58.3	83.3	NA	2.1	NR	
RCM	—	Amoxicillin 500 mg + Metronidazole 500 mg 3/Day 7d	3.8	80.0	40.0	0.4	2.6	66.7	• Current smokers • Disparity between groups at baseline • No postoperative professional prophylaxis • Short follow up
			2.5	54.0	23.0	0.6	1.1	23.1	
RCM	PDGF or EMD	Amoxicillin 500 mg 3/Day 7d	6.7	23.0	NA	0.9 (–)	3.6	NA	• Absence of group control • Highly variable follow-up • Unclear material and methods • Peri-implant defect configuration
RCM	-	Amoxicillin/clavulanic acid 875/125 mg + Metronidazole 250 mg 3/Day 10d	1.3	58.9	NR	NA	0.4	58.8	• Peri-implant defect configuration
CTG	EMD	-	5.4	80	80.0	0.1	4.3	56.6	• Peri-implant defect configuration • Addition of CTG in some cases • Strict SPT
RCM	—	Amoxicillin 750 mg 2/Day 7d	3.7	1.6 (mBI)[a]	59.2	2.5	2.2	85.2	• Peri-implant defect configuration • Absence of control group • Short follow up
RCM	—	—	4.2	70.6	88.2	1.3	3.7	70.6	• Absence of control group • Short follow up • Small sample size • Implant brand
—	EMD	Amoxicillin 375 mg + Metronidazole 250 mg 3/Day 8d	2.2	70.0	65.0	NA	1.1	75.0	• Current smokers • Absence of control group • Absence of PPD measurement
CTG (if needed)	—	Amoxicillin/clavulanic acid 1gr/200 mg 2/Day 6d	2.8	53.4	23.5	0.7	NA	45.3	• Implant brand (one) • Absence of radiographic measurement analysis
RCM	—	Amoxicillin 375 mg 3/day + Metronidazole 400 mg 2/Day 10d	4.2	67.7	NR	2.8	2.3	NR	• Absence of control group • Small sample size • No postoperative professional prophylaxis
RCM	—	—	1.6	38.9	NA	0.4	NA	NA	• Absence of demographic data • Absence of radiographic measurement analysis
			1.6	25.9		0.5			
			2.7	61.1		0.3			
ADM	-	Amoxicillin 500 mg 2/Day 10d	1.8	39.0	NR	NR	1.0	NA	• Short follow up • Small sample size • No postoperative professional prophylaxis
			2.6	31.0			1.2		

(Continues)

TABLE 4 (Continued)

Author (year)	Study design	Follow-up (months)	N patients (total)	N patients (sites)	Intervention	Defect configuration (number of walls)	Decontamination strategy	Healing protocol (submerged/ transmucosal)	Bone graft
Wen et al. (2021)[70]	PS	8	22	22 (32)	Reconstructive therapy	Circumferential	Implantoplasty + Glycine AP + Tetracycline (250 mg/2.5 cc)	Submerged	FDBA + DBBM + AB
Wiltfang et al. (2012)[32]	PCS	12	22	22 (36)	Reconstructive therapy	NR	Curettes + Diamonds + Implantoplasty + Etching gel	Transmucosal/ nonsubmerged	DBBM + AB
Yamamoto et al. (2021)[50]	PCS	12	12	12 (12)	Reconstructive therapy	2, 3, and circumferential	Er:YAG laser	Transmucosal/ nonsubmerged	DBBM

Abbreviations: AB, autogenous bone; ADM, absorbable acellular dermal matrix; AP, air-powder abrasive; CA, citric acid; CTG, connective tissue graft; DBBM, deproteinized bovine bone mineral; DBBMC, deproteinized bovine bone mineral collagen, HA, hydroxyapatite/tricalcium phosphate; dPTFE, titanium reinforced nonresorbable dense polytetrafluoroethylene; EDTA, 24% ethylenediaminetetraacetic acid; EMD, enamel matrix derivative protein; FDBA, freeze-dried bone allograft; NA, not assessed; NBDBS, nonbovine-derived bone substitute; NR, not reported; PC, prospective cohort study; PCS, prospective case series; PS, prospective controlled study; RCM, resorbable collagen membrane; RCS, retrospective case series; RCT, randomized controlled clinical trial; Ti, titanium; US, ultrasonic scaler device.

[a]Modified sulcular bleeding index (mBI) (Mombelli et al. 1987).

[b]Defect configuration classification (Schwarz et al. 2007).

7 | SIGNIFICANCE OF BONE GRAFTING MATERIAL

The use of bone grafting materials in the reconstructive therapy of peri-implantitis was empirically adopted from interventions related to bone regeneration of periodontal defects (Figures 2–4). Autogenous bone is derived from the same individual and therefore provides osteoconductivity (scaffold), osteoinductivity (growth factors), and osteogeneicity (mesenchymal cells). In this sense, it was identified that cortical bone chips supply 43 growth factors, such as TGF-β1, TGF-β2, BMP, and OSF-1, which are all critical in bone formation.[37] To reduce morbidity associated with a secondary harvesting site, other biomaterials have been advocated. Xenogeneic grafts, particularly anorganic bovine bone, have been extensively studied (Figure 5). It is a deproteinized, sterilized, slowly resorbable bovine cancellous bone. It was demonstrated that topographic features promote blood clot stabilization, and interconnected channels stimulate cell migration.[38] Accordingly, its function is merely osteoconductive. On the other hand, allogeneic grafts are sourced from human cadavers, and according to the preservation process, they may or may not provide osteoinductive potential.[39] In general, demineralized grafts are prone to display osteoinductivity as they preserve bone morphogenetic proteins (BMP).[40] In particular, BMP-2 and BMP-9 have been shown to orchestrate the modulation and differentiation of mesenchymal cells into bone-forming cells.[41–43] Regardless of the nature, the turnover of allogeneic grafts is, in general, significantly faster when compared to xenografts, resulting in a lower rate of residual particulated graft of the former.[44] Synthetic materials are biocompatible bone fillers that, ideally, should show minimal fibrotic reactions and undergo remodeling while supporting new bone formation (Figure 6).[45] Interestingly, in peri-implantitis therapy, porous titanium granules as synthetic material were suggested to support the process of reosseointegration.[21]

Several bone substitutes have been tested in this therapeutic modality, with xenografts and allografts being the most explored. There was considerable heterogeneity in terms of radiographic bone gain and disease resolution. For instance, Nart et al.[46] used a freeze-dried allograft combined with locally delivered antibiotics and found a mean radiographic bone gain of 3.6 mm, while Monaca et al.[35] found a bone gain of only 0.4 mm. This difference may be partially due to the follow-up durations (the latter was reported at the 5-year follow-up, while the former was reported at the 1-year follow-up). Xenografts have been used alone,[47,48] in combination with autogenous bone,[49] with 10% collagen,[29,36] and in combination with biologics.[33] In noncomparative studies, disease resolution ranged from 50%[50] to 85%[49] at the 12-month follow-up. Aghazadeh et al.[51] compared the use of autogenous bone to a xenograft. Interestingly, approximately 2x greater disease resolution and radiographic bone gain were found when xenografts were used. One report,[29] however, noted no significant differences in terms of bone gain or clinical resolution of peri-implantitis when collagenated xenografts were used compared to OFD. Roccuzzo et al.[36] using the same bone substitute achieved 45% disease resolution at the 60-month follow-up. Synthetic bone substitutes were further investigated. De Tapia et al.[52] evaluated the effect of hydroxyapatite/tricalcium phosphate in reconstructive therapy. When the surface was decontaminated with titanium brushes as a mechanical method, the mean disease resolution amounted to 66% with a radiographic bone gain of 2.6 mm. Thus, Schwarz et al.[53] compared hydroxyapatite and demineralized bovine bone combined with a collagen barrier membrane in a 6-month case series study. Comparable outcomes were achieved in terms of clinical

Barrier membrane	Biologic	Antibiotics	Probing depth reduction (mm)	Bleeding score reduction (%)	Suppuration reduction (%)	Mucosal recession (mm)	Radiographic bone gain (mm)	Disease resolution (%)	Confounders of disease resolution
dPTFE	–	Amoxicillin 500 mg 3/Day 10d or Azithromycin 250 mg 2/Day 3 days	2.9	63.3	NR	NA	3.4	NA	• Short follow up • Current smokers • History of periodontitis
–	–	Ampicillin/sulbactam 1.5gr i.v. or Clindamycin 600 mg (prophylactic)	4.0	36.0	72.0	1.3	3.5	NA	• No prosthesis removal during surgery • Unclear radiographic measurement analysis • Absence of demographic data
-	-	-	3.2	41.0	NR	NR	26.3 (%)	50.0	• Short follow up • Unknown SPT • Absence of control group • Absence of demographic data

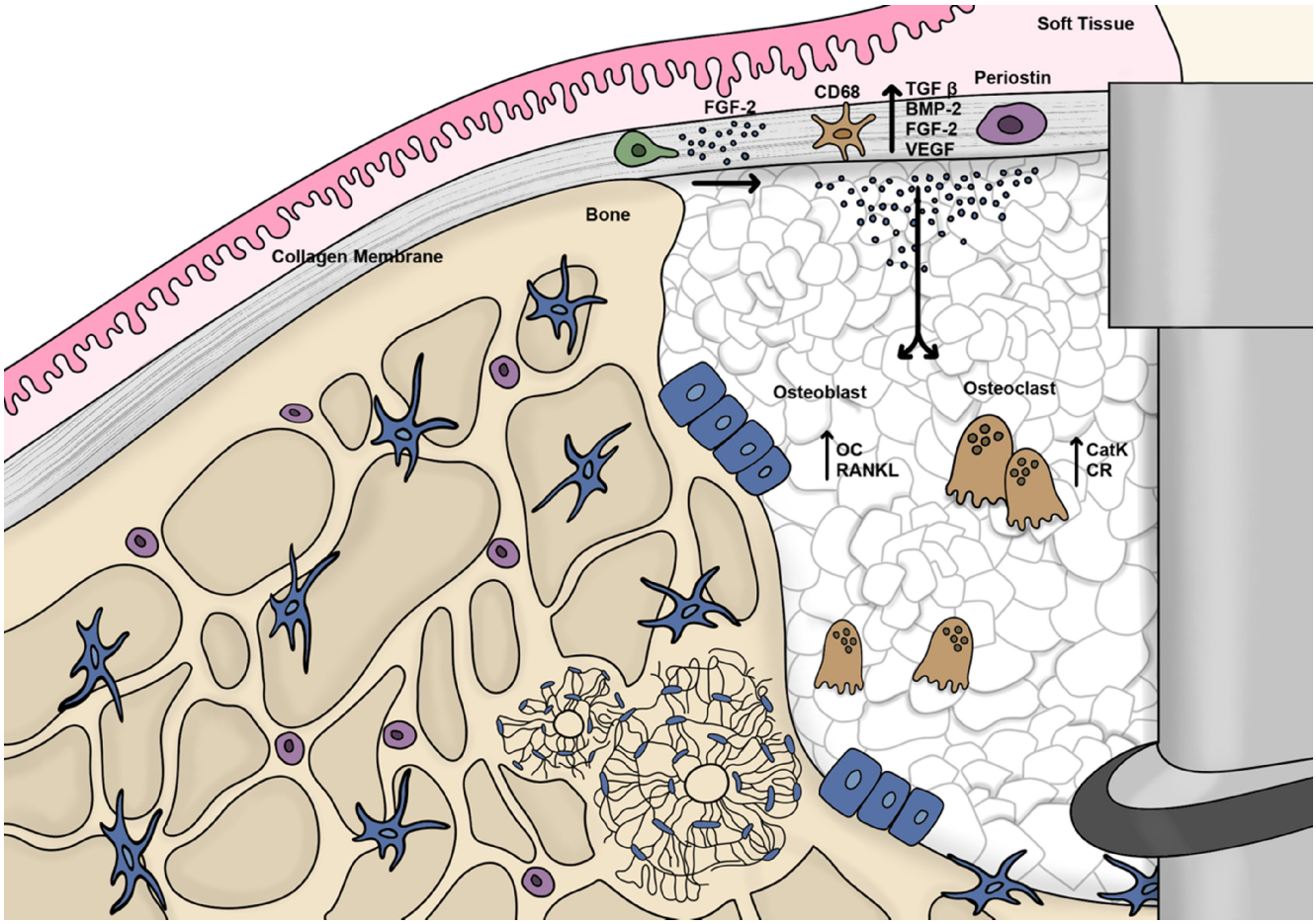


FIGURE 2 Schematic illustration of the cellular and molecular events of the inflammatory cascade during peri-implant regeneration in reconstructive therapy of peri-implantitis.

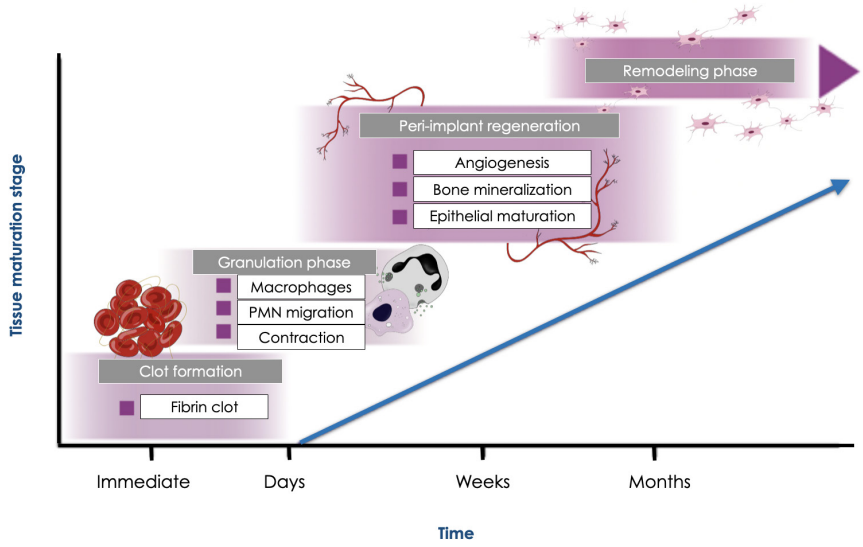


FIGURE 3 Cellular stages of regeneration after reconstructive therapy of peri-implantitis.

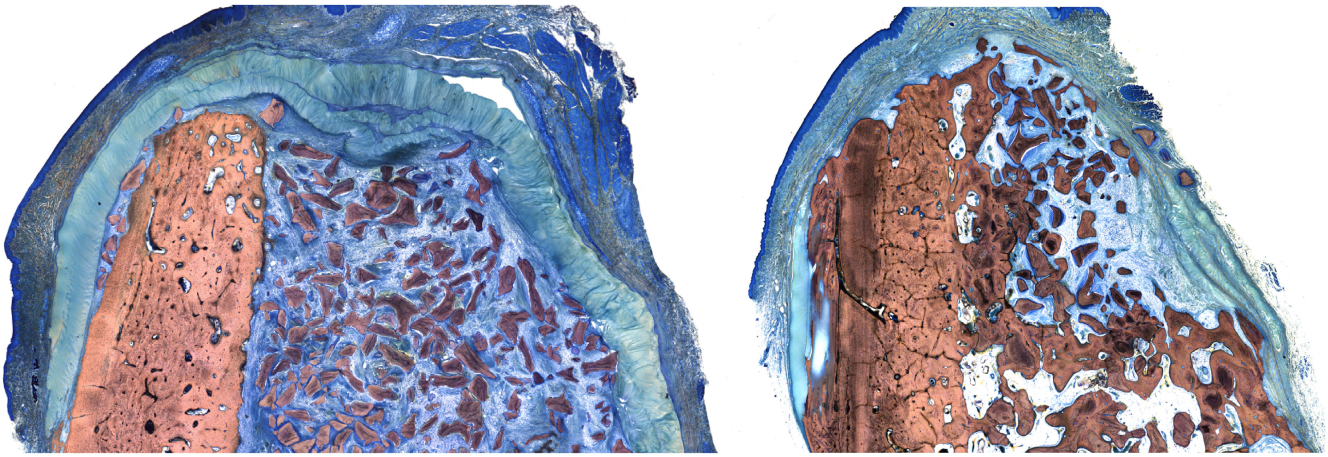


FIGURE 4 Histologic images at 4- and 24-week follow-up of a created alveolar bone defect reconstructive by means of xenograft and a sugar-based collagen matrix (Ossix Volumax, Datum Dental, Lod, Israel). Note the ossifying potential of the matrix, while excluding epithelial cells from the grafted area.

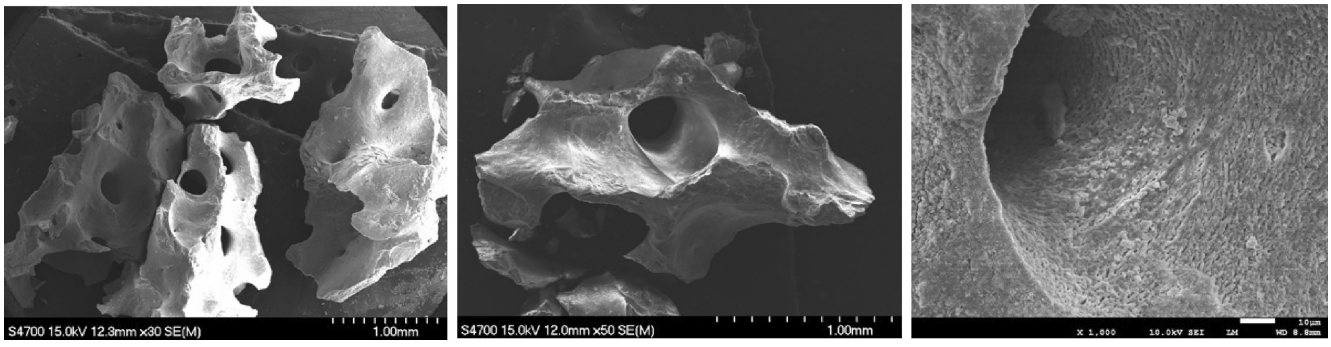


FIGURE 5 Scanning electron microscopy (SEM) of a bovine-derived particle (Inteross, SigmaGraft, CA, USA) at different magnifications (×30, ×50 and ×1000).

attachment level and PPD reduction. Moreover, titanium granules have been suggested as bone substitutes. Radiographic bone gain was outperformed when compared to control groups (OFD); however, disease resolution was, in general, low.[21,26] Therefore, the most suitable bone substitute for use in reconstructive therapy remains unclear.

8 | SIGNIFICANCE OF BIOLOGICAL AGENTS

Biologics are a group of agents or mediators that work through various mechanisms to promote tissue generation. These molecules promote a variety of essential cellular events in wound healing, including DNA

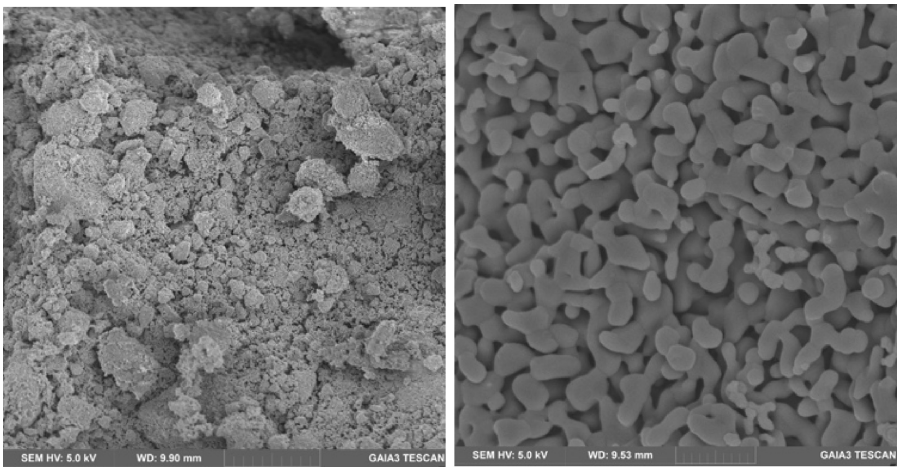


FIGURE 6 Scanning electron microscopy (SEM) of a synthetic material (tricalcium phosphate) (Bone Sigma TCP, SigmaGraft, CA, USA) at different magnifications (x30, x50, and x1000).

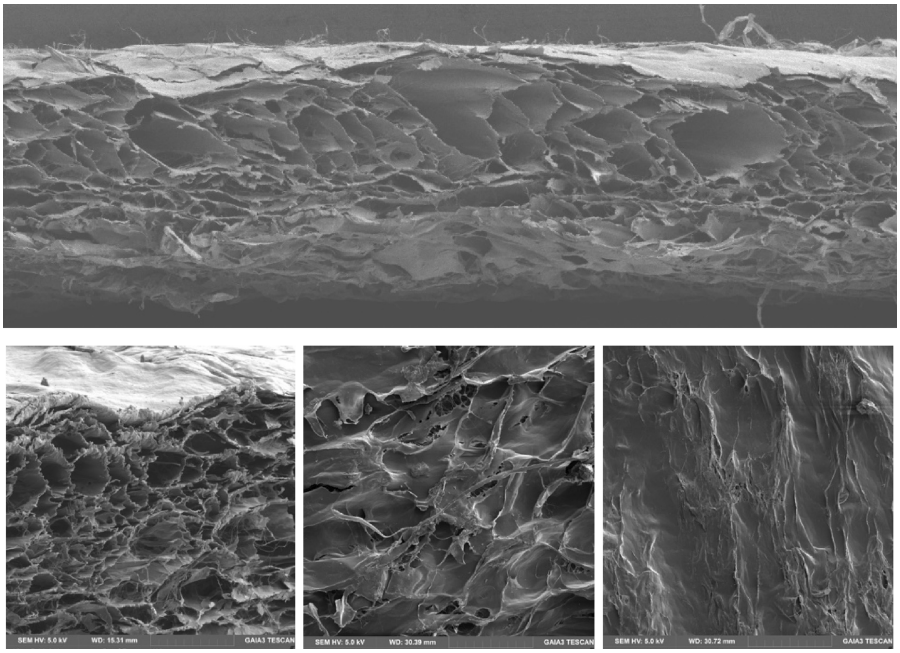


FIGURE 7 Scanning electron microscopy (SEM) of a collagen-based resorbable barrier membrane (InterCollagen Guide, SigmaGraft, CA, USA) at different magnifications (×800, ×1600, ×1600, and ×3200).

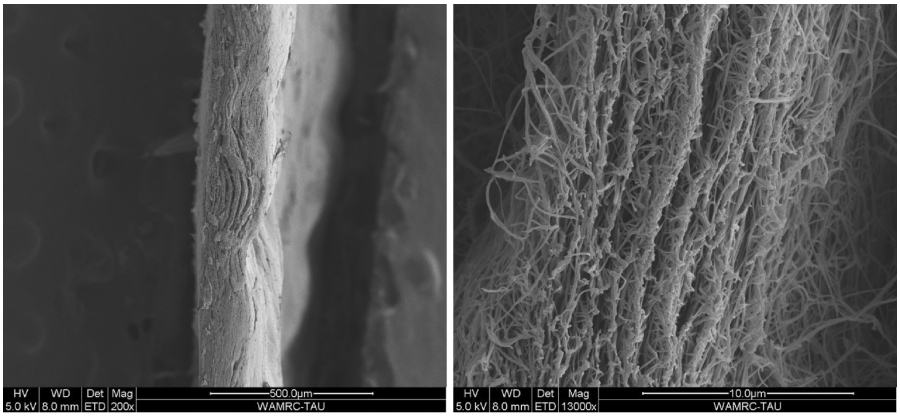


FIGURE 8 Scanning electron microscopy (SEM) cross-sectional view of a sugar-based cross-linking barrier membrane (Ossix Plus, Datum Dental, Lod, Israel) at different magnifications (200× and 13 000×).

synthesis, chemotaxis, cell differentiation, mitogenesis, and matrix biosynthesis. Consequently, these biologics have been utilized to enhance hard tissue regeneration procedures, enhance healing potential, and promote more rapid wound closure.[54,55] The use of biologics in the periodontal and implantology arenas has been extensively studied.[55,56]

Nevertheless, the literature on peri-implantitis therapy is sparse. Hamzacebi et al.[57] in an RCT compared OFD to OFD combined with platelet-rich fibrin (PRF) as a reconstructive agent. At the 6-month follow-up, PPD reduction (mean difference approximately 0.4 mm), gain in attachment (mean difference approximately 1.5 mm) and keratinized

TABLE 5 Comparative studies testing the effect of barrier membranes in reconstructive therapy for peri-implantitis.

Author (year)	Study design	Follow-up (months)	N patients (total)	N patients (sites)	Intervention	Defect configuration (number of walls)	Decontamination strategy	Healing protocol (submerged/ transmucosal)	Bone graft	Barrier membrane
Isler et al. (2022)[58]	RCT	36	51	25 (25) 26 (26)	Reconstructive therapy	2, 3 and 4	Ti curettes + Saline	Transmucosal/ nonsubmerged	DBBM	CGF RCM
Monje et al. (2023)[17]	RCT	12	33	17 (24) 16 (24)	Reconstructive therapy	2, 3 and 4	Ti brushes +3% Hydrogen peroxide + Saline	Transmucosal/ nonsubmerged	DMCA	– RCM
Regidor et al. (2023)[68]	RCT	12	43	22 (22) 21 (21)	Reconstructive therapy	1, 2, 3, and 4	Ti curettes + Ti brushes + Saline	Transmucosal/ nonsubmerged	DBBMC	– RCM
Roos- Jansåker et al. (2014)[66]	RCT	72	25	12 (22) 13 (23)	Reconstructive therapy	2, 3 and 4	3% Hydrogen peroxide + Saline	Transmucosal/ nonsubmerged	HA	- (PGA/PLABM)
Schwarz et al. (2009)[80]	CS	48	20	11 (11) 9 (9)	Reconstructive therapy	Semi/or circumferential	Plastic curettes + Saline	Transmucosal/ nonsubmerged	DBBM HA	RCM

Abbreviations: CGF, concentrated growth factor; CS, case series; DBBM, deproteinized bovine bone mineral; DBBMC, deproteinized bovine bone mineral collagen, HA, hydroxyapatite/tricalcium phosphate; DMCA, Demineralized and mineralized cortical allograft; NA, not assessed; NR, not reported; PGA/PLABM, pga/pla barrier membrane; RCM, resorbable collagen membrane; RCT, randomized controlled clinical trial; SPT, Supportive periodontal therapy; Ti, titanium.

[a]Modified sulcular bleeding index (mBI) (Mombelli et al. 1987).[81]

[b]Suppuration Index (Monje et al. 2020).[82]

mucosa gain favored the sites where PRF was used. For example, Isler et al.[58] tested the effectiveness of concentrated growth factors (CGFs) in combination with reconstructive therapy with the same intervention and a collagen membrane. At the 36-month follow-up, the use of the collagen membrane outperformed the use of CGF in terms of PPD reduction. Hence, the effectiveness of autogenous growth factors is controversial. However, Isehed et al.[28] compared EMD to OFD of angular peri-implant bone defects at the 60-month follow-up. It was demonstrated that radiographic bone level was superior in sites managed by means of reconstructive therapy (mean difference approximately 1 mm). Nevertheless, no significant differences were noted in the evaluated clinical parameters. A long-term case series study reported the use of EMD or platelet-derived growth factors (PDGF) as adjuncts to reconstructive therapy to manage advanced peri-implantitis bone defects. In a mean follow-up period of 48 months, a mean radiographic bone gain and clinical bone gain of 3.6 and 6.8 mm were noted, respectively. Therefore, the use of heterologous biologics is promising, but further investigations are warranted to better understand the added benefit of these to reconstructive therapy.

9 | SIGNIFICANCE OF THE BARRIER MEMBRANE

The term "guided bone regeneration" implies the use of barrier membranes to fulfil the principle of "compartmentalization" (Figures 7 and 8).[59] Hence, the barrier membrane aims to promote bone formation while acting as a passive barrier to preclude soft tissue ingrowth. Moreover, the effect of the barrier membrane has further been shown to promote bone formation, as it induces molecular and cellular events. Preclinical studies have demonstrated that the use of nonresorbable barrier membranes enhances the levels of Runx2-positive osteoprogenitor cells, osteocalcin, alkaline phosphatase, osteopontin, and sialoprotein.[60–62] In fact, barrier membranes have been shown to promote the expression of tissue by increasing matrix metallopeptidases 2 and 9 along with interleukins 1 and 6.[61] Studies assessing the effect of resorbable (collagen-based) membranes on bone expression have noted that there is an increase in osteocalcin, cathepsin K and receptor activator of nuclear kappa-β factor.[62] This type of membrane hosts different cell phenotypes that progressively secrete major bone-related growth factors such as bone morphogenetic protein-2.[62] Therefore, the function of the barrier membrane is not merely to exclude undesired cells but also to accelerate de novo bone formation.

Hürzeler et al., in a preclinical model, validated the beneficial use of bone grafting combined with barrier membrane to enhance radiographic bone level.[63] This approach has further been proven beneficial in case series and cohort studies.[23,46,49,64,65] Therefore, as noted, reconstructive therapy seems beneficial in general lines. Now, the issue that needs to be addressed is the added benefit of using a barrier membrane to fulfill the principle of guided bone regeneration. In a 60-month follow-up study, Ross-Jansåker et al.[66] noted no remarkable clinical or radiographic differences in sites reconstructed by means of an algae-derived bone grafting material with (1.3 mm) or without barrier membrane (1.1 mm). In contrast,

Biologic	Antibiotics	Probing depth reduction (mm)	Bleeding score reduction (%)	Suppuration reduction (%)	Mucosal recession (mm)	Radiographic bone gain (mm)	Disease resolution (%)	Confounders of disease resolution (bullets)
-	Amoxicillin 500 mg and Metronidazole 500 mg 3/Day 7d	2.1 2.1	56.8 61.8	NR NR	0.3 0.4	1.4 1.7	26.9 34.6	• Number of reinstrumentations during follow-up period • History of periodontitis • Current smokers
—	Amoxicillin 750 mg 2/Day 7d	4.0 3.4	1.49 (mBI)[a] 1.50 (mBI)[a]	0.56 (±0.65)[b] 0.56 (±0.66)[b]	0.13 0.25	1.7 1.7	79.2 75.1	• Strict adherence to SPT • Contained defects within bony housing
—	Amoxicillin 750 mg 2/Day 10d	4.2 4.5	66.2 68.4	16.6 48.8	0.1 0.2	0.9 1.4	45.0 36.8	• Number of reinstrumentations during follow-up period • Time interval recalls • Peri-implant defect morphology
-	Amoxicillin 375 mg 3/day and Metronidazole 400 mg 2/Day 10d	3.3 3.0	82.9 42.3	22.7 19.9	2.0 1.3	1.1 1.3	51.1 51.1	• Disparity between groups at baseline • Current smokers • History of periodontitis
-	-	2.5 1.1	51.0 32.0	NR NR	0.5 0.4	NA NA	NA NA	• Implant brand • Peri-implant defect morphology • Absence of radiographic measurement analysis

Schwarz et al.[67] in a 48-month study showed an enhancement in clinical and radiographic parameters that favored the use of collagen membrane when compared to the use of nanocrystalline hydroxyapatite alone. In agreement, Isler et al.[58] in a 36-month clinical trial demonstrated the outperformance of bone grafting combined with a collagen membrane (1.7 mm) when compared to the use of anorganic bovine bone grafting combined with concentrated growth factors (1.4 mm) in reconstructive therapy. Monje et al.[17] indicated that cross-linked barrier membranes do not exert an influence on the clinical and radiographic variables. In fact, radiographic bone gain was similar for sites reconstructed by means of allografts combined with membrane and for sites grafted but where barrier membrane was not used (1.7 mm). Regidor et al.[68] tested the adjunctive effect of a collagen membrane to an anorganic bovine bone with 10% collagen in a 12-month follow-up trial. Radiographic bone gain and PPD reduction amounted to 1.2 and 4.4 mm, respectively. No significant differences in disease resolution were achieved. It is interesting to note, however, that postoperative complications such as soft tissue dehiscence and exposure of the particulate bone graft and/or membrane were recorded for the test sites. Longer surgical times (approximately10 min) and higher levels of self-reported pain at 2 weeks were further observed in the test group. It is worth noting that there are variables that might be key in understanding the above-listed findings. For instance, there was high heterogeneity in the defect configurations, type of bone grafting materials, and implant position. Featuring bone morphology is relevant considering that the number of residual walls along with implant position in the bucco-lingual perspective dictate continence.[8,69] Moreover, the nature of bone grafting materials may further influence the stability achievable by the graft itself within the bone defect. While particulated materials are less prone to stabilization, other presentations, such as fibers or collagenated materials, might promote space maintenance in a more effective manner. Hence, although comparative studies do not suggest the adjunct use of barrier membranes; it may rely upon the stability achievable by the bone grafting material (Table 5 Figures 9–11).

Concerning the nature of the membrane, most of the studies assessing reconstructive measures reported the use of resorbable membranes.[8,22,24,31,49] Other authors, instead, included in their surgical protocol the use of nonresorbable membranes. Wen et al.[70] in a prospective cohort study applied reconstructive therapy by means of a composite bone graft and a nonresorbable membrane (dPTFE) in a submerged healing approach. At 8 months, the clinical bone gain reported at re-entry was ~3.5 mm. Nevertheless, the main shortcomings derived from this approach are the high risk of exposure of the nonresorbable membrane and associated postoperative complications (i.e., infection) or the disturbance of the mucosal margin (i.e., reduction of the vestibular depth and the buccal band of keratinized mucosa).

10 | SIGNIFICANCE OF THE HEALING APPROACH

Limited evidence exists to date using the submerged healing approach for the surgical management of peri-implantitis. Roos-Jansaker

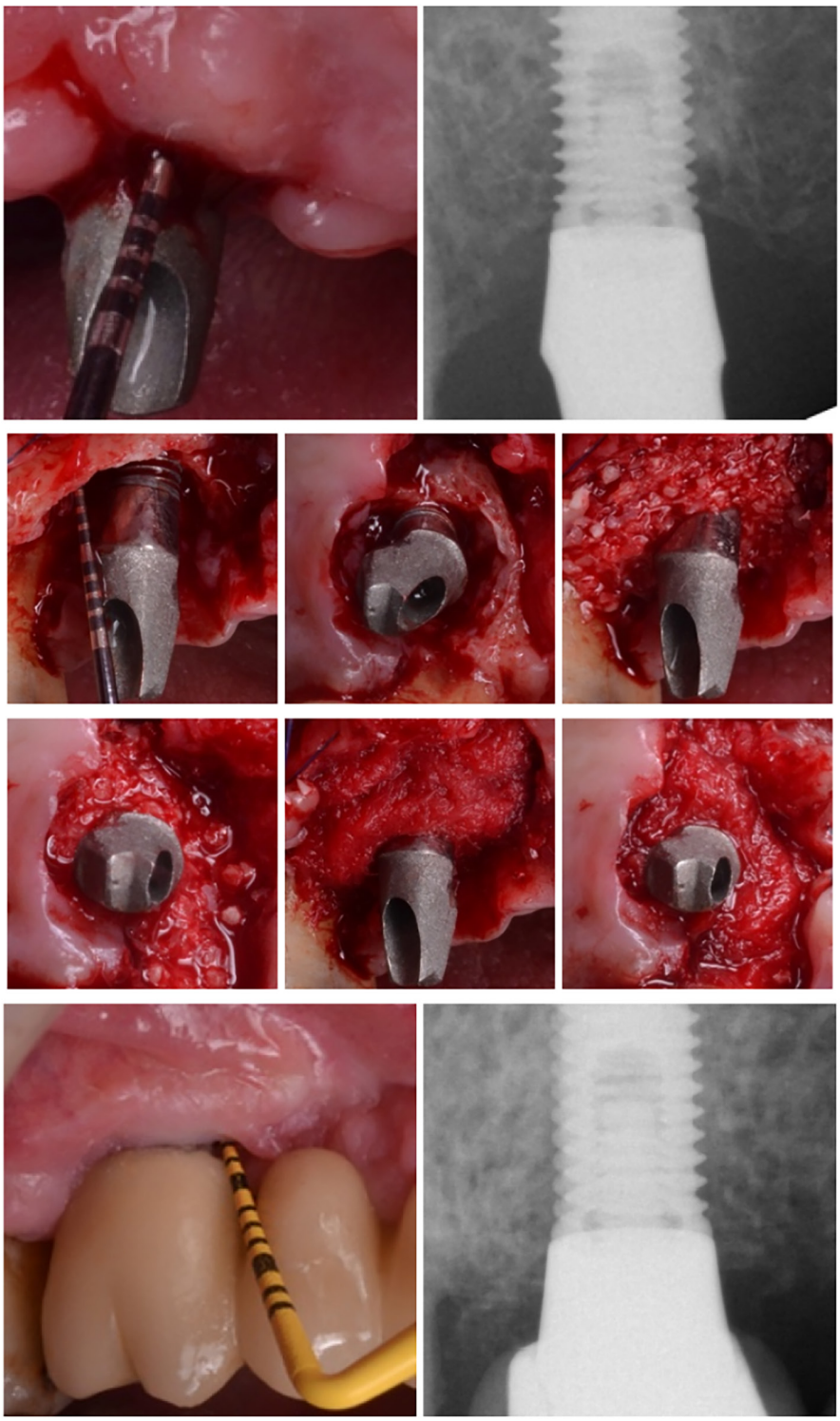


FIGURE 9 Moderate intrabony peri-implantitis defect (class Ic) managed by means of mineralized and demineralized allografts applying a transmucosal healing approach. Clinical and radiographic images at the 24-month follow-up showed clinical health and radiographic bone gain.

et al.[31] in a case series demonstrated that applying reconstructive therapy and submerged healing for 6 months, a reduction of PPD by 4.2 mm and a mean defect fill of 2.3 mm were achievable. Significantly less optimal outcomes were obtained in the same group[71] when applying nonsubmerged healing. Monje et al.[49] showed that the defect depth and PPD were reduced by 2.2 and 3.7 mm, respectively. Schlee et al.[72] in an 18-month study showed that submerged healing for 6 months resulted in ~3 mm of radiographic bone gain. Schwarz et al.[73] in a preclinical study demonstrated that submerged healing improved the surgical treatment outcome in terms of radiographic and histomorphometric findings (bone-to-implant contact). Again, the primary drawbacks of this technique are that to promote submerged healing, the prosthesis must be removed in advance of surgical therapy, and placement should not be performed <4 months after surgery. Moreover, primary intention healing may lead to a distortion of the mucosal margin and a reduction in the keratinized

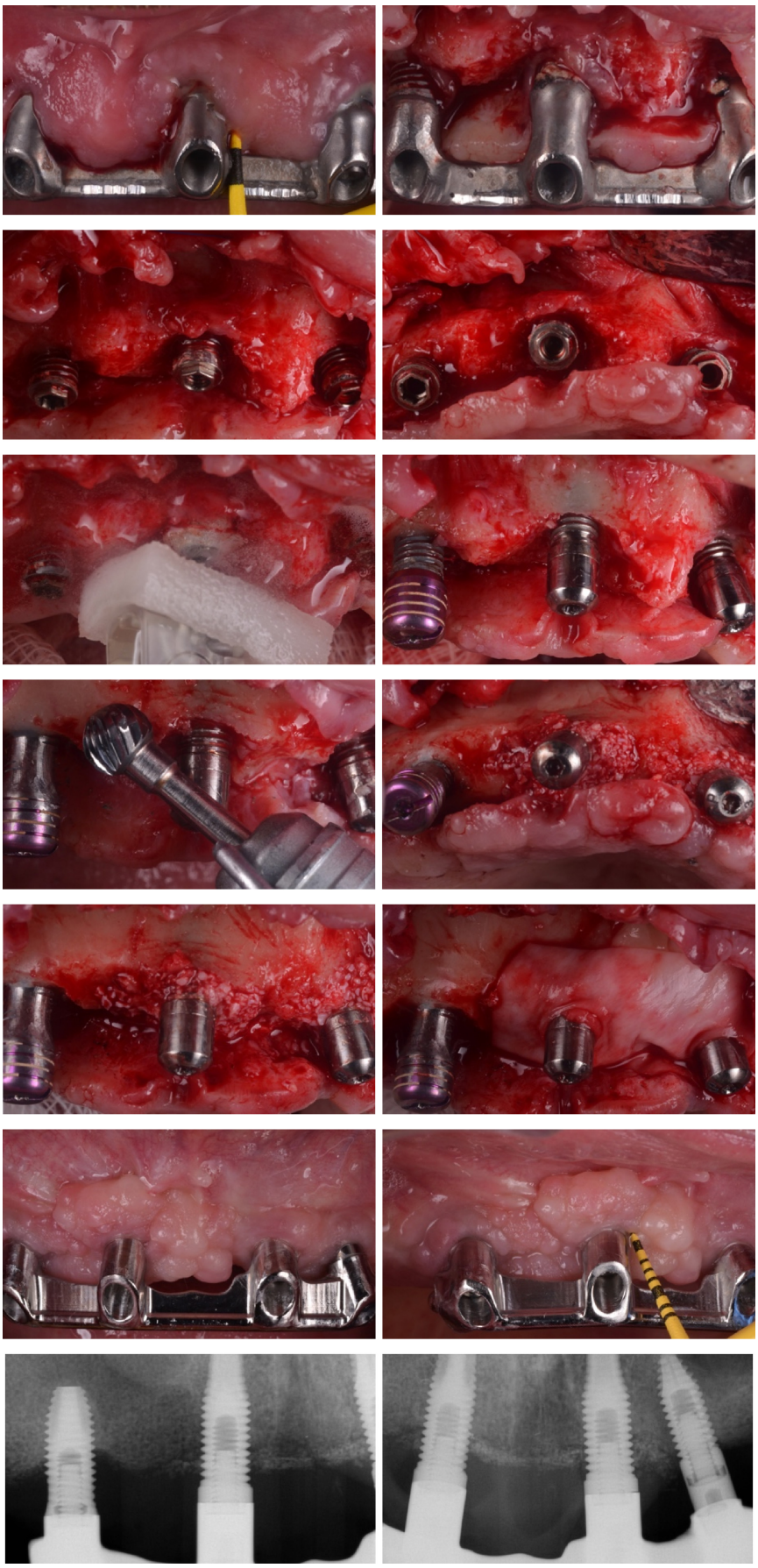


FIGURE 10 Moderate combined peri-implantitis defects (class IIIb) managed by means of combined therapy. A mixture of autogenous bone and xenografts was used as the grafting material. Due to the partial continence of the bone defect, a collagen barrier membrane was used. Note peri-implant health and radiographic bone gain at the 24-month follow-up.

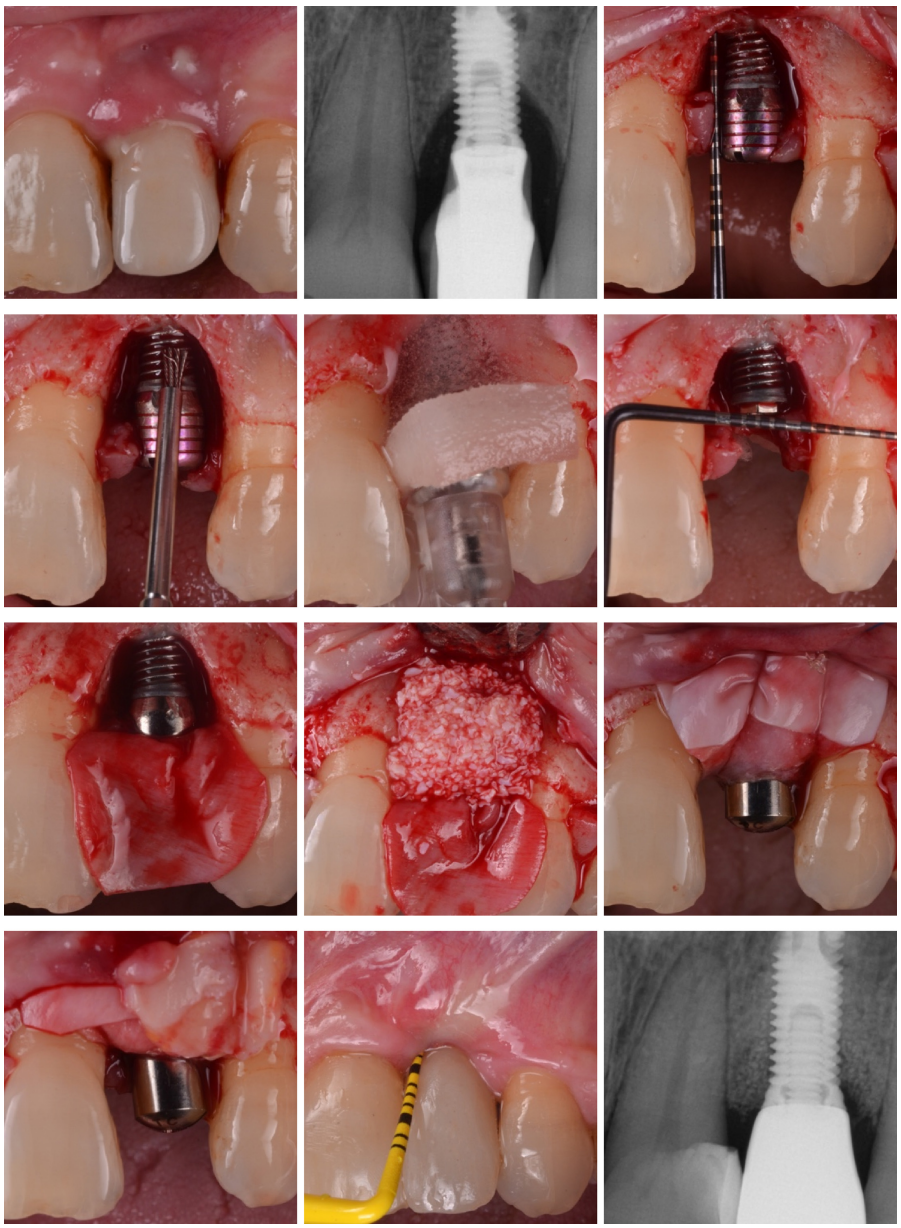


FIGURE 11 Moderate peri-implantitis bone defect (class Ib) in the esthetic area. Surface decontamination was performed by means of an electrolytic approach. Reconstructive therapy was carried out in terms of a mixture of autogenous bone and xenograft in an equal ratio. A barrier membrane to enhance the stability of the graft and a connective tissue graft to minimize mucosal recession were used as adjuncts. Peri-implant health and radiographic bone gain were noted at the 12-month follow-up.

mucosa. Hence, even though it may offer some benefits, transmucosal (nonsubmerged) healing seems to be more practical for the patient and the operator.

11 | CONCLUDING REMARKS

Reconstructive therapy is effective to gain radiographic bone level and to establish a healthy peri-implant condition. Therefore, in scenarios exhibiting contained/angular defects, the application of bone grafting materials may assist in arresting the disorder while increasing the support and minimizing mucosal recession. However, the most effective bone substitute for reconstructive therapy is unclear. The application of barrier membranes, nevertheless, does not seem to enhance the outcome of well-contained defects. Nonetheless, their use in partially contained defects remains debatable. Furthermore, the use of biologics is promising, even though there is limited evidence regarding their effectiveness in peri-implantitis therapy.

ACKNOWLEDGMENTS

The authors thank Dr. Ryan Noh (University of Toronto, Toronto, Canada) for the illustrations. The illustrations were sponsored by the Department of Periodontology, Universitat Internacional de Catalunya, Barcelona, Spain.)

CONFLICT OF INTEREST STATEMENT

The authors have no direct conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Monje A, Insua A, Wang HL. Understanding peri-implantitis as a plaque-associated and site-specific entity: on the local predisposing factors. *J Clin Med*. 2019;8(2):279.
2. Blanco C, Linares A, Dopico J, et al. Peri-implantitis, systemic inflammation, and dyslipidemia: a cross-sectional biochemical study. *J Periodontal Implant Sci*. 2021;51:342-351.
3. Chaushu L, Tal H, Sculean A, Fernandez-Tome B, Chaushu G. Peri-implant disease affects systemic complete blood count values-an experimental in vivo study. *Clin Oral Investig*. 2020;24:4531-4539.
4. Figuero E, Graziani F, Sanz I, Herrera D, Sanz M. Management of peri-implant mucositis and peri-implantitis. *Periodontol 2000*. 2000;2014(66):255-273.
5. Listl S, Fruhauf N, Dannewitz B, et al. Cost-effectiveness of non-surgical peri-implantitis treatments. *J Clin Periodontol*. 2015;42:470-477.
6. Hentenaar DFM, De Waal YCM, Van Winkelhoff AJ, Meijer HJA, Raghoebar GM. Non-surgical peri-implantitis treatment using a pocket irrigator device; clinical, microbiological, radiographical and patient-centred outcomes-a pilot study. *Int J Dent Hyg*. 2020;18:403-412.
7. Faggion CM Jr, Chambrone L, Listl S, Tu YK. Network meta-analysis for evaluating interventions in implant dentistry: the case of peri-implantitis treatment. *Clin Implant Dent Relat Res*. 2013;15:576-588.
8. Schwarz F, Sahm N, Schwarz K, Becker J. Impact of defect configuration on the clinical outcome following surgical regenerative therapy of peri-implantitis. *J Clin Periodontol*. 2010;37:449-455.
9. Aghazadeh A, Persson RG, Renvert S. Impact of bone defect morphology on the outcome of reconstructive treatment of peri-implantitis. *Int J Implant Dent*. 2020;6:33.
10. Galarraga-Vinueza ME, Obreja K, Magini R, Sculean A, Sader R, Schwarz F. Volumetric assessment of tissue changes following combined surgical therapy of peri-implantitis: a pilot study. *J Clin Periodontol*. 2020;47:1159-1168.
11. Lagervall M, Jansson LE. Treatment outcome in patients with peri-implantitis in a periodontal clinic: a retrospective study. *J Periodontol*. 2013;84:1365-1373.
12. de Waal YC, Raghoebar GM, Meijer HJ, Winkel EG, van Winkelhoff AJ. Prognostic indicators for surgical peri-implantitis treatment. *Clin Oral Implants Res*. 2016;27:1485-1491.
13. Ravida A, Siqueira R, Di Gianfilippo R, et al. Prognostic factors associated with implant loss, disease progression or favorable outcomes after peri-implantitis surgical therapy. *Clin Implant Dent Relat Res*. 2022;24:222-232.
14. Monje A, Kan JY, Borgnakke W. Impact of local predisposing/precipitating factors and systemic drivers on peri-implant diseases. *Clin Implant Dent Relat Res*. 2022;25:640-660.
15. Monje A, Amerio E, Cha JK, et al. Strategies for implant surface decontamination in peri-implantitis therapy. *Int J Oral Implantol (Berl)*. 2022;15:213-248.
16. Monje A, Mesquita PF. Clinical considerations in the surgical management of peri-implantitis lesions in the esthetic zone. *J Esthet Restor Dent*. 2023;35(3):457-466.
17. Monje A, Pons R, Vilarrasa J, Nart J, Wang HL. Significance of barrier membrane on the reconstructive therapy of peri-implantitis: a randomized controlled trial. *J Periodontol*. 2023;94:323-335.
18. Tsitoura E, Tucker R, Suvan J, Laurell L, Cortellini P, Tonetti M. Baseline radiographic defect angle of the intrabony defect as a prognostic indicator in regenerative periodontal surgery with enamel matrix derivative. *J Clin Periodontol*. 2004;31:643-647.
19. Tonetti MS, Pini-Prato G, Cortellini P. Periodontal regeneration of human intrabony defects. IV. Determinants of healing response. *J Periodontol*. 1993;64:934-940.
20. Monje A, Schwarz F. Principles of combined surgical therapy for the management of peri-implantitis. *Clin Adv Periodontics*. 2022;12:57-63.
21. Jepsen K, Jepsen S, Laine ML, et al. Reconstruction of peri-implant osseous defects: a multicenter randomized trial. *J Dent Res*. 2016;95:58-66.
22. Renvert S, Giovannoli JL, Roos-Jansaker AM, Rinke S. Surgical treatment of peri-implantitis with or without a deproteinized bovine bone mineral and a native bilayer collagen membrane: a randomized clinical trial. *J Clin Periodontol*. 2021;48:1312-1321.
23. Wen SC, Barootchi S, Wang HL, Huang WX. Non-submerged reconstructive approach for peri-implantitis osseous defect with removal of implant crowns: one-year outcomes of a prospective case series study. *J Periodontol*. 2022;93:1250-1261.
24. Monje A, Pons R, Amerio E, Wang HL, Nart J. Resolution of peri-implantitis by means of implantoplasty as adjunct to surgical therapy: a retrospective study. *J Periodontol*. 2022;93:110-122.
25. Schwarz F, John G, Schmucker A, Sahm N, Becker J. Combined surgical therapy of advanced peri-implantitis evaluating two methods of surface decontamination: a 7-year follow-up observation. *J Clin Periodontol*. 2017;44:337-342.
26. Wohlfahrt JC, Lyngstadaas SP, Ronold HJ, et al. Porous titanium granules in the surgical treatment of peri-implant osseous defects: a randomized clinical trial. *Int J Oral Maxillofac Implants*. 2012;27:401-410.
27. Andersen H, Aass AM, Wohlfahrt JC. Porous titanium granules in the treatment of peri-implant osseous defects-a 7-year follow-up study. *Int J Implant Dent*. 2017;3:50.
28. Isehed C, Svenson B, Lundberg P, Holmlund A. Surgical treatment of peri-implantitis using enamel matrix derivative, an RCT: 3- and 5-year follow-up. *J Clin Periodontol*. 2018;45:744-753.
29. Derks J, Ortiz-Vigon A, Guerrero A, et al. Reconstructive surgical therapy of peri-implantitis: a multicenter randomized controlled clinical trial. *Clin Oral Implants Res*. 2022;33:921-944.
30. Deppe H, Horch HH, Neff A. Conventional versus CO_2 laser-assisted treatment of peri-implant defects with the concomitant use of pure-phase beta-tricalcium phosphate: a 5-year clinical report. *Int J Oral Maxillofac Implants*. 2007;22:79-86.
31. Roos-Jansaker AM, Renvert H, Lindahl C, Renvert S. Submerged healing following surgical treatment of peri-implantitis: a case series. *J Clin Periodontol*. 2007;34:723-727.
32. Wiltfang J, Zernial O, Behrens E, Schlegel A, Warnke PH, Becker ST. Regenerative treatment of peri-implantitis bone defects with a combination of autologous bone and a demineralized xenogenic bone graft: a series of 36 defects. *Clin Implant Dent Relat Res*. 2012;14:421-427.
33. Mercado F, Hamlet S, Ivanovski S. Regenerative surgical therapy for peri-implantitis using deproteinized bovine bone mineral with 10% collagen, enamel matrix derivative and doxycycline-a prospective 3-year cohort study. *Clin Oral Implants Res*. 2018;29:583-591.
34. Froum SJ, Kim SW. Regenerative treatment of advanced peri-implantitis: a retrospective case series with 3 to 15 years of follow-up. *Int J Periodontics Restorative Dent*. 2022;42:623-629.
35. La Monaca G, Pranno N, Annibali S, Cristalli MP, Polimeni A. Clinical and radiographic outcomes of a surgical reconstructive approach in the treatment of peri-implantitis lesions: a 5-year prospective case series. *Clin Oral Implants Res*. 2018;29:1025-1037.
36. Roccuzzo M, Mirra D, Pittoni D, Ramieri G, Roccuzzo A. Reconstructive treatment of peri-implantitis infrabony defects of various configurations: 5-year survival and success. *Clin Oral Implants Res*. 2021;32:1209-1217.

37. Caballe-Serrano J, Bosshardt DD, Buser D, Gruber R. Proteomic analysis of porcine bone-conditioned medium. *Int J Oral Maxillofac Implants*. 2014;29:1208-1215d.
38. Galindo-Moreno P, Abril-Garcia D, Carrillo-Galvez AB, et al. Maxillary sinus floor augmentation comparing bovine versus porcine bone xenografts mixed with autogenous bone graft. A split-mouth randomized controlled trial. *Clin Oral Implants Res*. 2022;33:524-536.
39. Monje A, O'Valle F, Monje-Gil F, et al. Cellular, vascular, and Histomorphometric outcomes of solvent-dehydrated vs freeze-dried allogeneic graft for maxillary sinus augmentation: a randomized case series. *Int J Oral Maxillofac Implants*. 2017;32:121-127.
40. Urist MR. A morphogenetic matrix for differentiation of bone tissue. *Calcif Tissue Res*. 1970;4(Suppl):98-101.
41. Fujioka-Kobayashi M, Sawada K, Kobayashi E, Schaller B, Zhang Y, Miron RJ. Recombinant human bone morphogenetic protein 9 (rhBMP9) induced osteoblastic behavior on a collagen membrane compared with rhBMP2. *J Periodontol*. 2016;87:e101-e107.
42. Fujioka-Kobayashi M, Schaller B, Saulacic N, Zhang Y, Miron RJ. Growth factor delivery of BMP9 using a novel natural bovine bone graft with integrated atelo-collagen type I: biosynthesis, characterization, and cell behavior. *J Biomed Mater Res A*. 2017;105:408-418.
43. Saulacic N, Schaller B, Munoz F, et al. Recombinant human BMP9 (RhBMP9) in comparison with rhBMP2 for ridge augmentation following tooth extraction: an experimental study in the beagle dog. *Clin Oral Implants Res*. 2018;29:1050-1059.
44. Serrano Mendez CA, Lang NP, Caneva M, Ramirez Lemus G, Mora Solano G, Botticelli D. Comparison of allografts and xenografts used for alveolar ridge preservation. A clinical and histomorphometric RCT in humans. *Clin Implant Dent Relat Res*. 2017;19:608-615.
45. Moore WR, Graves SE, Bain GI. Synthetic bone graft substitutes. *ANZ J Surg*. 2001;71:354-361.
46. Nart J, de Tapia B, Pujol A, Pascual A, Valles C. Vancomycin and tobramycin impregnated mineralized allograft for the surgical regenerative treatment of peri-implantitis: a 1-year follow-up case series. *Clin Oral Investig*. 2018;22:2199-2207.
47. Obreja K, Galarraga-Vinueza ME, Muller K, Begic A, Ramanauskaite A, Schwarz F. Volumetric tissue changes following combined surgical therapy of peri-implantitis: a 2-year follow-up analysis. A prospective case series. *Clin Implant Dent Relat Res*. 2022;24:267-275.
48. Schwarz F, Sahm N, Iglhaut G, Becker J. Impact of the method of surface debridement and decontamination on the clinical outcome following combined surgical therapy of peri-implantitis: a randomized controlled clinical study. *J Clin Periodontol*. 2011;38:276-284.
49. Monje A, Pons R, Roccuzzo A, Salvi GE, Nart J. Reconstructive therapy for the management of peri-implantitis via submerged guided bone regeneration: a prospective case series. *Clin Implant Dent Relat Res*. 2020;22:342-350.
50. Yamamoto A, Kubota T, Komatsu Y, et al. Efficacy of erbium:YAG laser for regenerative surgical treatment of peri-implantitis: clinical, microbiological, and biomarker analyses. *Int J Periodontics Restorative Dent*. 2021;41:187-192.
51. Aghazadeh A, Persson GR, Stavropoulos A, Renvert S. Reconstructive treatment of peri-implant defects-results after three and five years. *Clin Oral Implants Res*. 2022;33:1114-1124.
52. de Tapia B, Mozas C, Valles C, Nart J, Sanz M, Herrera D. Adjunctive effect of modifying the implant-supported prosthesis in the treatment of peri-implant mucositis. *J Clin Periodontol*. 2019;46:1050-1060.
53. Schwarz F, Bieling K, Latz T, Nuesry E, Becker J. Healing of intrabony peri-implantitis defects following application of a nanocrystalline hydroxyapatite (Ostim) or a bovine-derived xenograft (bio-Oss) in combination with a collagen membrane (bio-Gide). A case series. *J Clin Periodontol*. 2006;33:491-499.
54. Avila-Ortiz G, Ambruster J, Barootchi S, et al. American Academy of periodontology best evidence consensus statement on the use of biologics in clinical practice. *J Periodontol*. 2022;93:1763-1770.
55. Suarez-Lopez Del Amo F, Monje A. Efficacy of biologics for alveolar ridge preservation/reconstruction and implant site development: an American Academy of periodontology best evidence systematic review. *J Periodontol*. 2022;93:1827-1847.
56. Tavelli L, Chen CJ, Barootchi S, Kim DM. Efficacy of biologics for the treatment of periodontal infrabony defects: an American Academy of periodontology best evidence systematic review and network meta-analysis. *J Periodontol*. 2022;93:1803-1826.
57. Hamzacebi B, Oduncuoglu B, Alaaddinoglu EE. Treatment of peri-implant bone defects with platelet-rich fibrin. *Int J Periodontics Restorative Dent*. 2015;35:415-422.
58. Isler SC, Soysal F, Ceyhanli T, Bakirarar B, Unsal B. Efficacy of concentrated growth factor versus collagen membrane in reconstructive surgical therapy of peri-implantitis: 3-year results of a randomized clinical trial. *Clin Oral Investig*. 2022;26:5247-5260.
59. Melcher AH. On the repair potential of periodontal tissues. *J Periodontol*. 1976;47:256-260.
60. Tanaka S, Matsuzaka K, Sato D, Inoue T. Characteristics of newly formed bone during guided bone regeneration: analysis of cbfa-1, osteocalcin, and VEGF expression. *J Oral Implantol*. 2007;33:321-326.
61. Lima LL, Gonçalves PF, Sallum EA, Casati MZ, Nociti FH Jr. Guided tissue regeneration may modulate gene expression in periodontal defects: a human study. *J Periodontal Res*. 2008;43:459-464.
62. Turri A, Elgali I, Vazirisani F, et al. Guided bone regeneration is promoted by the molecular events in the membrane compartment. *Biomaterials*. 2016;84:167-183.
63. Hurzeler MB, Quinones CR, Morrison EC, Caffesse RG. Treatment of peri-implantitis using guided bone regeneration and bone grafts, alone or in combination, in beagle dogs. Part 1: clinical findings and histologic observations. *Int J Oral Maxillofac Implants*. 1995;10:474-484.
64. Froum SJ, Froum SH, Rosen PS. A regenerative approach to the successful treatment of peri-implantitis: a consecutive series of 170 implants in 100 patients with 2- to 10-year follow-up. *Int J Periodontics Restorative Dent*. 2015;35:857-863.
65. Schwarz F, Sculean A, Bieling K, Ferrari D, Rothamel D, Becker J. Two-year clinical results following treatment of peri-implantitis lesions using a nanocrystalline hydroxyapatite or a natural bone mineral in combination with a collagen membrane. *J Clin Periodontol*. 2008;35:80-87.
66. Roos-Jansaker AM, Persson GR, Lindahl C, Renvert S. Surgical treatment of peri-implantitis using a bone substitute with or without a resorbable membrane: a 5-year follow-up. *J Clin Periodontol*. 2014;41:1108-1114.
67. Isler SC, Soysal F, Ceyhanli T, Bakirarar B, Unsal B. Regenerative surgical treatment of peri-implantitis using either a collagen membrane or concentrated growth factor: a 12-month randomized clinical trial. *Clin Implant Dent Relat Res*. 2018;20:703-712.
68. Regidor E, Ortiz-Vigón A, Romandini M, Dionigi C, Derks J, Sanz M. The adjunctive effect of a resorbable membrane to a xenogeneic bone replacement graft in the reconstructive surgical therapy of peri-implantitis: a randomized clinical trial. *J Clin Periodontol*. 2023;50(6):765-783.
69. Rosen PS, Froum SJ, Sarmiento H, Wadhawani CP. A revised peri-implantitis classification scheme: adding three-dimensional considerations to facilitate prognosis and treatment planning. *Int J Periodontics Restorative Dent*. 2022;42:291-299.
70. Wen SC, Barootchi S, Huang WX, Wang HL. Surgical reconstructive treatment for infraosseous peri-implantitis defects with a submerged healing approach: a prospective controlled study. *J Periodontol*. 2022;93:195-207.

71. Roos-Jansaker AM, Lindahl C, Persson GR, Renvert S. Long-term stability of surgical bone regenerative procedures of peri-implantitis lesions in a prospective case-control study over 3 years. *J Clin Periodontol*. 2011;38:590-597.
72. Schlee M, Wang HL, Stumpf T, Brodbeck U, Bosshardt D, Rathe F. Treatment of periimplantitis with electrolytic cleaning versus mechanical and electrolytic cleaning: 18-month results from a randomized controlled clinical trial. *J Clin Med*. 2021;10(16):3475.
73. Schwarz F, Jepsen S, Herten M, Sager M, Rothamel D, Becker J. Influence of different treatment approaches on non-submerged and submerged healing of ligature induced peri-implantitis lesions: an experimental study in dogs. *J Clin Periodontol*. 2006;33:584-595.
74. Polymeri A, Anssari-Moin D, van der Horst J, Wismeijer D, Laine ML, Loos BG. Surgical treatment of peri-implantitis defects with two different xenograft granules: a randomized clinical pilot study. *Clin Oral Implants Res*. 2020;31:1047-1060.
75. Renvert S, Roos-Jansaker AM, Persson GR. Surgical treatment of peri-implantitis lesions with or without the use of a bone substitute-a randomized clinical trial. *J Clin Periodontol*. 2018;45:1266-1274.
76. Astolfi V, Gomez-Menchero A, Rios-Santos JV, et al. Influence of removing or leaving the prosthesis after regenerative surgery in peri-implant defects: retrospective study: 32 clinical cases with 2 to 8 years of follow-up. *Int J Environ Res Public Health*. 2021;18(2):645.
77. de Tapia B, Valles C, Ribeiro-Amaral T, et al. The adjunctive effect of a titanium brush in implant surface decontamination at peri-implantitis surgical regenerative interventions: a randomized controlled clinical trial. *J Clin Periodontol*. 2019;46:586-596.
78. Pilenza D, Filippi A, Walter C, Zitzmann NU, Bornstein MM, Kuhl S. Surgical therapy of peri-implantitis with adjunctive hydroxyapatite and enamel matrix derivative: a 1-year retrospective case series. *Swiss Dent J*. 2022;132:238-246.
79. Wang CW, Ashnagar S, Gianfilippo RD, Arnett M, Kinney J, Wang HL. Laser-assisted regenerative surgical therapy for peri-implantitis: a randomized controlled clinical trial. *J Periodontol*. 2021;92:378-388.
80. Schwarz F, Sahm N, Bieling K, Becker J. Surgical regenerative treatment of peri-implantitis lesions using a nanocrystalline hydroxyapatite or a natural bone mineral in combination with a collagen membrane: a four-year clinical follow-up report. *J Clin Periodontol*. 2009;36:807-814.
81. Mombelli A, Muhle T, Bragger U, Lang NP, Burgin WB. Comparison of periodontal and peri-implant probing by depth-force pattern analysis. *Clin Oral Implants Res*. 1997;8:448-454.
82. Monje A, Vera M, Munoz-Sanz A, Wang HL, Nart J. Suppuration as diagnostic criterium of peri-implantitis. *J Periodontol*. 2021;92:216-224.

How to cite this article: Monje A, Pons R, Nart J, Miron RJ, Schwarz F, Sculean A. Selecting biomaterials in the reconstructive therapy of peri-implantitis. *Periodontol 2000*. 2023;00:1-21. doi:10.1111/prd.12523