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HUMAN RANDOMIZED CONTROL TRIAL

Significance of barrier membrane on the reconstructive therapy of peri-implantitis: A randomized controlled trial

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Abstract

Background: The objective of this trial was to investigate the clinical and radiographic significance of using a mixture of mineralized and demineralized allografts in combination (M) or not (NM) with a resorbable cross-linked barrier membrane in the reconstructive therapy of peri-implantitis defects.

Methods: A two-arm randomized clinical trial was performed in patients diagnosed with peri-implantitis that exhibited contained defects. Clinical parameters were recorded at baseline (T_0), 6 months (T_1), and 12 months (T_2). Radiographic parameters were recorded at T_0 and T_2. A composite criterion for disease resolution was defined a priori. A generalized linear model of repeated measures with generalized estimation equation statistical methods was used.

Results: Overall, 33 patients ($n_{\text{implants}} = 48$) completed the study. At T_2, mean disease resolution was 77.1%. The use of a barrier membrane did not enhance the probability of disease resolution at T_2 (odds ratio [OR] = 1.55, $p = 0.737$). Conversely, the odds of disease resolution were statistically associated with the modified plaque index recorded at T_0 (OR = 0.13, $p = 0.006$) and keratinized mucosa width (OR = 2.10, $p = 0.035$). Moreover, women exhibited greater odds to show disease resolution (OR = 5.56, $p = 0.02$).

Conclusion: Reconstructive therapy by means of a mixture of mineralized and demineralized allografts is effective in clinically resolving peri-implantitis and in gaining radiographic marginal bone level. The addition of a barrier membrane to reconstructive therapy of peri-implantitis does not seem to enhance the outcomes of contained bone defects (NCT05282667).

KEYWORDS
biocompatible materials, dental implants, jaw, peri-implantitis, regeneration, wound healing

1 | INTRODUCTION

Peri-implantitis represents a biofilm-mediated inflammatory condition associated with progressive bone loss.[1] This entity may compromise the longevity of dental implants, thus impacting negatively the quality of life of patients. In addition, peri-implantitis has been suggested to lead to an increased systemic status of inflammation.[2,3] This may rise the susceptibility to experience life-threating conditions such as acute myocardial infarction or liver disease.[2] Therefore, peri-implantitis lesions must be promptly eliminated. To achieve such a goal, the clinician can opt to remove the infected dental implant[4] or to decontaminate it along with the performance of other maneuvers to establish a healthy ecosystem and to minimize the risk of recolonization.[5] Although implant removal is the most predictable strategy to resolve the condition, it may not satisfy patient demands concerning function, chewing, aesthetics, and phonetics.[6] On the other hand, treatment of peri-implantitis proved being less predictable but more conservative, less time-consuming, and less costly when compared to implant removal and providing a new implant-supported rehabilitation.[7]

The therapeutic modality relies primarily upon the operator's perspective, implant position, soft tissue characteristics, and defect configuration. Nonsurgical measures have been shown to be unsatisfactory in terms of disease resolution.[8] Surgical strategies, on the other hand, demonstrated enhanced predictability and effectiveness levels in the long-term stability of the peri-implant hard and soft tissues.[9] In general lines, peri-implantitis bone defects exhibiting contained defects are prone to show favorable reconstructive outcomes together with a consistent reduction in pocket depth.[10,11] Multiple clinical trials have validated this approach alone[12–14] or in combination with other measures such as implantoplasty[15,16] in combined defects exhibiting supracrestal components. It is worth noting that no consensus or solid evidence exists regarding the use and type of biomaterials and barrier membranes. In this sense, in a 12-month randomized clinical trial, Renvert et al. showed the radiographic benefit in terms of increased support of bone grafting combined with a barrier membrane when compared with no grafting.[13] Hürzeler et al. validated the beneficial use of bone grafting combined with barrier membrane to enhance radiographic bone level in the reconstructive management of peri-implantitis.[17] Recently, Derks et al. yielded no marked differences, except in mucosal recession (MR), when comparing reconstructive therapy only by means of bone grafting with open flap debridement.[18] Into the bargain, Ross-Jansåker et al. noted no remarkable clinical or radiographic differences in sites reconstructed by means of bone grafting with or without barrier membrane in a 5-year follow-up.[19] In contrast, in a 3-year clinical trial, Isler et al. demonstrated the outperformance of bone grafting combined with barrier membrane when compared to the use of bone grafting combined with concentrated growth factors in reconstructive therapy.[20] In light of the heterogeneous findings and the scant data concerning the added benefit of using barrier membranes in the reconstructive therapy of peri-implantitis, the goal of the present randomized clinical trial is to assess the clinical and radiographic significance of using a mixture of mineralized and demineralized allografts in combination (M) or not (NM) with a resorbable cross-linked collagen barrier membrane.

2 | MATERIALS AND METHODS

A prospective randomized controlled two-arm study was conducted in accordance with the Declaration of Helsinki on human studies, following approval from the ethics committee of the University of Extremadura (Badajoz). Patients were collected at the CICOM-MONJE Institute (Badajoz, Spain). Patients received and signed a written informed consent. Patient data were anonymized. The study was registered and approved by www.clinicaltrials.gov (NCT05282667). The study is reported in accordance with the CONSORT statement.[21]

2.1 | Study sample

Consecutive patients exhibiting peri-implantitis were recruited from April 2019 up to June 2021. An a priori sample size was calculated considering 37% as the difference in disease resolution between study groups.[22] Using this estimation with an alpha risk of 0.05% and a statistical power of 80% led to a sample size of 31 patients. Considering a potential dropout rate of 15%, a total of 36 patients (18 per group) were recruited. The following criteria were applied: all patients aged 18–80 years, nonsmokers, with no presence of infectious diseases at the time of implant placement or during the maintenance program, with no presence of systemic disease or medication known to alter bone metabolism, and partially/completely edentulous patients who had no active periodontal disease. Moreover, patients with peri-implantitis bone defects where reconstructive therapy was indicated due to contained defect configuration combined or not with supracrestal defect configuration were included (i.e., type Ib, Ic, IIIb, and IIIc).[23] Subjects were excluded due to pregnancy or lactation, former (<10 years) or current smoking, and uncontrolled medical conditions. Patients with

uncontained defects (i.e., supracrestal bone defects—type II, or implants outside of the bony envelope—type Ia or IIIa)[23] where reconstructive therapy was not indicated, patients with sites with <2 mm of keratinized mucosa (KM) at the buccal aspect, or patients with implants outside of the bony housing based upon intraoperative visualization[24] were excluded.

2.2 | Randomization

Patients were randomly assigned to the test or control group according to the last digit of their chart number. As such, patients with records ending in 1–4 and 5–9 were included in the test group and control group, respectively. When the total sample size of any of the groups was reached, patients were only recruited for the remaining groups to complete the total sample size.

2.3 | Case definition of peri-implantitis

Peri-implantitis was defined according to the 2017 World Workshop of Periodontal and Peri-implant diseases.[25] Hence, the case definition applied was as follows: presence of bleeding and/or suppuration (SUP) on gentle probing (~0.2N), probing pocket depths (PPD) of ≥6 mm, bone levels ≥3 mm apical of the most coronal portion of the intraosseous part of the implant based on periapical X-ray. If the examiner deemed the access unsuitable, the prosthesis was retrieved for accurate diagnosis.

2.4 | Clinical assessment

The following clinical parameters and indices were recorded at T_0 (5–6 weeks after nonsurgical therapy), 6 months, and 12 months by one previously calibrated (intraoperative k value > 85% based on a previous examination of 15% of the overall sample) examiner (A.M.):

- PPD recorded in millimeter using a plastic/metal North Carolina probe applying an approximate probing force of 0.2 N.[13]
- Modified sulcular bleeding index (mSBI) that scored 0–3 according to the extensiveness and severity of bleeding on probing.[26]
- Modified plaque index (mPI) that scored 0–3 according to the visibility and severity of plaque accumulation.[26]
- MR was defined as the distance in millimeter from the implant–abutment connection as a steady mark and the mucosal margin.
- KM around dental implants, measured from the free mucosal margin to the mucogingival junction at the mid-buccal position, to the nearest millimeter, using a North Carolina probe.
- SUP index around implants applied according to the grade of SUP: grade 0 = no SUP or nonsuppurative exudate; grade 1 = SUP manifesting ≥15 s after gentle probing or SUP at a single spot (dot); grade 2 = SUP manifesting < 15 s after gentle probing or profuse SUP (drop or line), forming a confluent line; grade 3 = spontaneous SUP manifesting through the peri-implant sulcus upon palpation/compression of the peri-implant soft tissues.[27]
- Intraosseous component (IC) was measured intraoperatively at the mesial, medial, and distal aspect of the defect from the adjacent bony peak to the base of the defect using a North Carolina probe.

2.5 | Definition of disease resolution

Disease resolution was evaluated at the last examination. Peri-implantitis was considered resolved if the following case definition was present:

- Absence or one spot of (not profuse) bleeding and/or SUP on gentle probing (~0.2 N)
- PPD of ≤5 mm
- No radiographic progressive bone loss with a standard error of ≥1 mm[28]

2.6 | Radiographic assessment

Periapical radiographs were taken applying the long-cone paralleling technique assisted by the intraoral radiographic positioning system. The following radiographic variables were recorded at T_0 (baseline) and at the last follow-up examination T_2 (12 months) and were determined by a blinded examiner (R.P.):

- Marginal bone level (MBL): distance determined by taking linear measurements from the most mesial and distal point of the implant platform to the crestal bone on each periapical radiograph, corrected according to the known implant pitch.
- Defect width (WD): distance (mm) between the distal and mesial interproximal bone crest and the implant surface.
- Defect angulation (DA): angle resulting from a vertical line along the outer implant surface and a line extending along the peri-implant bone defect.

2.7 | Peri-implantitis bone defect morphology and severity

The characterization of peri-implantitis defects was based on defect morphology (classes I–III) and severity (grades S-M-A), as proposed elsewhere.[23] Briefly, according to morphology, the defects were classified as follows: class I—intraosseous defect (class Ib- 2- to 3-wall defect, class Ic- circumferential defect) and class III—combined defect (class IIIb- 2- to 3-wall defects + horizontal bone loss; class IIIc—circumferential defect + horizontal bone loss). Regarding severity, bone defects were graded as slight (S) (<25% of the implant length), moderate (M) (25%–50% of the implant length), and advanced (A) (>50% of the implant length).

2.8 | Nonsurgical therapy phase

Oral hygiene instructions were given as part of the diagnostic phase. All eligible patients diagnosed with peri-implantitis underwent nonsurgical therapy at least 5–6 weeks prior to the surgical reconstructive phase by one operator (A.M.). Briefly, ultrasonic debridement with a metal tip[*], a "mini-five" curette[†], and site-specific Gracey curettes[‡] were used for scaling and debridement of the peri-implant sulcus. Further submucosal air polishing was performed with erythritol-powder using a special plastic tip[§]. Irrigation was profusely applied with chlorhexidine 0.12%.[¶] Clinical assessment was performed to check resolution. If peri-implantitis was resolved, the patient was excluded from the study. Candidates for reconstructive therapy had healing abutments placed ≥2 weeks before the surgical reconstructive phase whenever possible.

2.9 | Surgical reconstructive therapy phase

A full-thickness flap was raised to have sufficient access. Debridement of granulation tissue was conducted subsequently using a "mini-five" curette[#], site-specific Gracey curettes[||], and NiTi brushes[**]. The surgical approach was tailored to the scenario. Implantoplasty was performed whenever uncontained components were present with a tungsten carbide bur[††]. Surface decontamination was performed by means of NiTi brushes[‡‡] for about 2–3 min at 600 rpm, followed by hydrogen peroxide (3%) for 2 min and irrigation with saline. The intraosseous compartments were grafted using a demineralized (fibers) and mineralized (particulated) cortical allograft[§§] up to the adjacent bony peaks. The test group (M group) received a cross-linked collagen membrane[¶¶] on the top of the stratified grafting material, while in the control group (NM group), no membrane was used, and the demineralized fibers were left in contact with the soft tissues. Nylon 5.0[##] was used for suturing. All the sites were left for transmucosal (nonsubmerged) healing.

2.10 | Postoperative care

Patients were prescribed to apply three times a day chlorhexidine and chitosan gel in the area for 2 weeks[||||], and systemic amoxicillin, 750 mg in two tablets a day for 7 days, was also prescribed. Moreover, anti-inflammatory medication (Ibuprofen, 600 mg, one tablet every 5–6 h for 5 days) was prescribed. After 2–3 weeks, the sutures were removed and oral hygiene resumed. At this stage, the dental hygienists performed full-mouth supramucosal supportive measures using an air polisher.[***] Prostheses were placed on the implants ≥4 weeks after the surgical intervention.

2.11 | Recall program

During the first 2 months after suture removal, patients were recalled for professional oral hygiene measures in the grafted area every 2-3 weeks until the third month after surgery. If proper oral hygiene was precluded by the faulty restorative access with interproximal brushes, modification of the prosthesis design was made until the access was satisfying. All the patients enrolled in the present study adhered thereafter to a 3-month recall peri-implant maintenance therapy program supervised by the

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[‡] Hu-Friedy, Chicago, Illinois.
[§] Air-Flow; EMS, Herrliberg, Switzerland.
[¶] Perioaid; Dentaid, Barcelona, Spain.
[#] Hu-Friedy, Chicago, Illinois.
[||] Hu-Friedy, Chicago, Illinois.
[**] Hans Korea Co., Gyenonggi-do, Korea.
[††] Meisinger LLC, Nauss, Germany.
[‡‡] Hans Korea Co., Gyenonggi-do, Korea.
[§§] LifeNet Health, Virginia Beach, Virginia.
[¶¶] RTM; Osteogenics Biomedical, Lubbock, Texas.
[##] Resorba Sutures; Osteogenics Biomedical, Lubbock, Texas.
[||||] Bexident Post; Isdin, Barcelona, Spain.
[***] Air-Flow; EMS, Herrliberg, Switzerland.

principal investigator during the first year after surgery (T_F).

2.12 | Statistical analysis

Absolute and relative frequencies and means and SD were used to describe the categorical and continuous variables, respectively. The homogeneous distribution of variables between study groups was analyzed through Pearson chi-squared and Mann–Whitney tests. A generalized linear model of repeated measures with generalized estimation equations (GEE) was performed to contrast intragroup differences of clinical and radiographic variables from T_0 to T_1, T_1 to T_2, and T_0 to T_2. p values were obtained with Bonferroni's correction. Simple binary logistic regression models with GEE were performed to explain the probability of disease resolution at T_2 follow-up depending on the study group (M vs. NM) and other potential clinical/radiographic independent variables. Unadjusted estimates of OR and 95% confidence intervals (CI) were obtained from Wald's chi-squared statistic. A multiple model was further constructed to adjust the results for all the relevant independent variables ($p < 0.10$) from the simple regression model. Simple linear regression models with GEE were carried out to estimate the magnitude of PPD changes from T_0 to T_2 according to the study group (M vs. NM) and other potential clinical/radiographic independent variables. Unadjusted estimates of beta coefficients (β) and 95% CI were obtained. Again, a multiple model was created to adjust the results for all the consistent independent variables ($p < 0.10$) from the simple regression models. The same strategy was applied for other dependent clinical and radiographic variables such as changes from T_0 to T_2 MBL, msBI, SUP, KM width, mPI, MR, WD, and DA. The analysis was performed with SPSS 15.0 (SPPS Inc., Chicago, Illinois). The significance level used was 5% ($\alpha = 0.05$).

3 | RESULTS

3.1 | Study population

A flowchart of this study is presented in Figure 1. From the 104 patients that were screened for eligibility, 64 did not meet the inclusion criteria, and four did not need surgical therapy due to earlier disease resolution by means of nonsurgical therapy. Among the 36 enrolled patients with a total of 51 implants, half of them were randomly allocated in the M group ($n = 18$) and the other half in the NM group ($n = 18$). At T_2, a total of 33 ($n_{implants} = 48$) patients (M = 17; NM = 16) completed the study.

3.2 | Demographics

The description of the main patient and implant variables is summarized in Table S1 (see online *Journal of Periodontology*). The mean age of the participants was 64 ± 9.3 years. Overall, 60.6% were female. The average of implants treated per patient was 1.5 ± 0.6. Almost half of the surgical reconstructive procedures were performed in the posterior upper arch (54.2%). Most of the treated implants in the NM group had an anodized surface (75%), while 41.7% of the implants in the M group included an acid-etched surface. Homogeneous distribution among the study groups was noted (see Table S1 in online *Journal of Periodontology*).

3.3 | Significance of barrier membrane on disease resolution

At T_2, disease resolution was reached in 75.1% (IC 95%: 53.3, 90.2%) and 79.2% (IC 95%: 57.9, 92.9%) of the surgical sites treated in the M and NM group, respectively (Figure 2). Mean disease resolution was 77.1%. The multiple logistic regression model confirmed that the use of a barrier membrane did not enhance the probability of disease resolution at T_2 (OR = 1.55, $p = 0.737$) (Table S2, see online *Journal of Periodontology*). Conversely, the odds of disease resolution were statistically associated with mPI recorded at T_0 (OR = 0.13, $p = 0.006$) and KM width (OR = 2.10, $p = 0.035$). In other words, one additional score of mPI recorded at T_0 reduced the overall probability of disease resolution to 87%, while one additional millimeter of KM width recorded at T_0 increased the chances of disease resolution up to 110% (Figure 3). Moreover, women exhibited greater odds to show disease resolution (OR = 5.56, $p = 0.02$).

Overall, the clinical parameters assessed proved significant changes from T_0 to T_2 ($p < 0.001$). Mean PPD reduction from T_0 to T_2 amounted to 3.41 ± 1.15 and 4.03 ± 1.47 mm in the M and NM group, respectively (Table 1). The findings from the linear regression models evidenced that the use of a barrier membrane was not significantly associated with a PPD reduction at T_2 ($\beta = 0.21$, $p = 0.292$) (Table S2). Indeed, mean PPD decrease was 0.21 mm higher in the NM compared to the M group. Nevertheless, the amount of PPD reduction was significantly related to the magnitude of PPD recorded at T_0 ($\beta = -0.93$, $p < 0.001$) and to the severity of the radiographic bone defect ($p = 0.039$). Particularly, one additional millimeter in PPD at T_0 was associated with 0.93 mm higher PPD reduction at T_2, while advanced radiographic bone defects displayed 1 mm of higher PPD reduction compared to slight bone defects ($\beta = -1.01$, $p = 0.031$) (Figure 4).

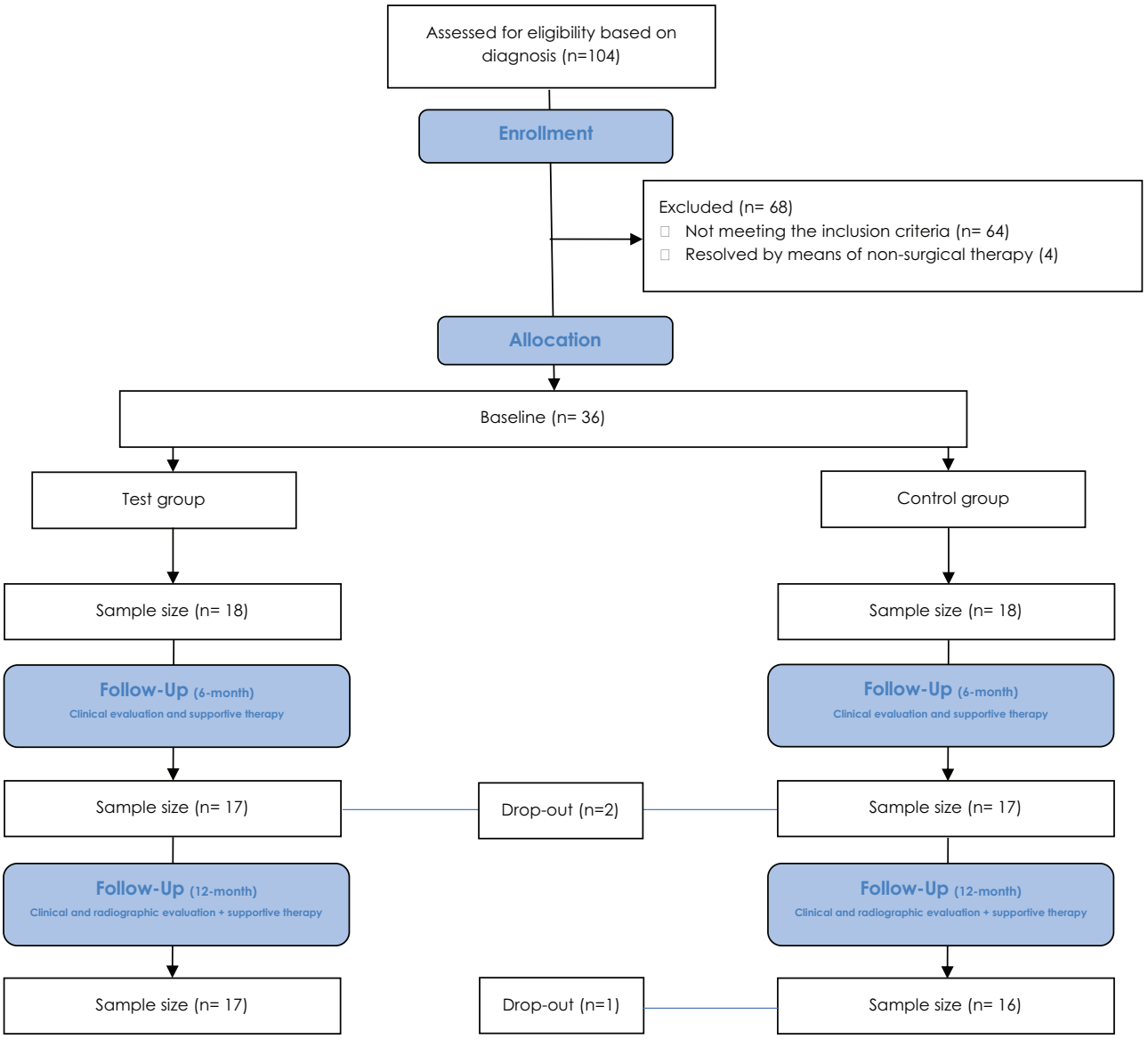

FIGURE 1 Flowchart of the study

Likewise, all the radiographic parameters examined were subjected to significant changes ($p < 0.001$). From T_0 to T_2 months, mean radiographic bone gain was 1.72 ± 0.72 and 1.73 ± 0.83 mm in the M and NM group, respectively (Table 1). The linear regression models also indicated that the role of the barrier membrane in MBL gain was negligible ($\beta = 0.07$, $p = 0.774$) (see Table S2 in online *Journal of Periodontology*). Interestingly, peri-implant DA at T_0 was the only variable linked with greater MBL gain at T_2 ($\beta = -0.03$, $p = 0.001$) (Figure 5). In detail, one positive grade (°) of DA recorded at T_0 was associated with 0.03 mm less MBL gain at T_2 (see Table S3 in online *Journal of Periodontology*)

The results obtained from the simple linear regression models evidenced that the use of a barrier membrane did not influence the T_0 to T_2 changes of any other potential clinical/radiographic parameters such as msBI ($\beta = -0.01$, $p = 0.960$), SUP ($\beta = 0.01$, $p = 0.974$), KM width ($\beta = -0.15$, $p = 0.785$), mPI ($\beta = -0.37$, $p = 0.059$), MR ($\beta = 0.21$, $p = 0.470$), WD ($\beta = 0.39$, $p = 0.155$), or DA ($\beta = -2.01$, $p = 0.601$).

4 | DISCUSSION

4.1 | Principal findings

The leading feature that dictates the therapeutic modality of peri-implantitis is bone defect configuration. Reconstructive therapy, in contrast to resective therapeutic

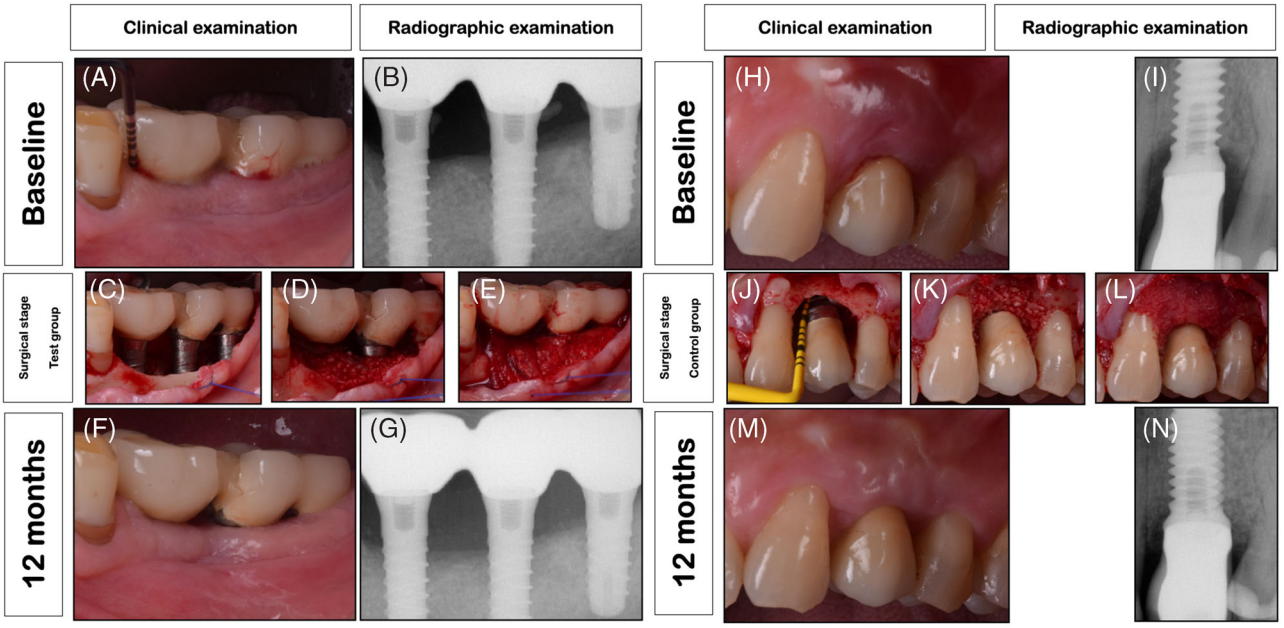

FIGURE 2 Case 1. Test group (M): (**A, B**) Initial presentation. (**C**) Full-thickness flap was elevated to complete the debridement of the granulation tissue and decontaminate the implant surface. (**D**) Reconstructive therapy was performed by means of mineralized and demineralized allograft. (**E**) A cross-link membrane was placed on the top and adapted to the defect. (**F, G**) Disease resolution and MBL gain was noted at T_2. Case 2. Control group (NM): (**H, I**) Initial presentation. (**J**) Full-thickness flap was elevated to complete the debridement of the granulation tissue and decontaminate the implant surface. (**K, L**) Reconstructive therapy was performed by means of mineralized and demineralized allograft. (**M, N**) Disease resolution and MBL gain were noted at T_2. MBL, marginal bone level

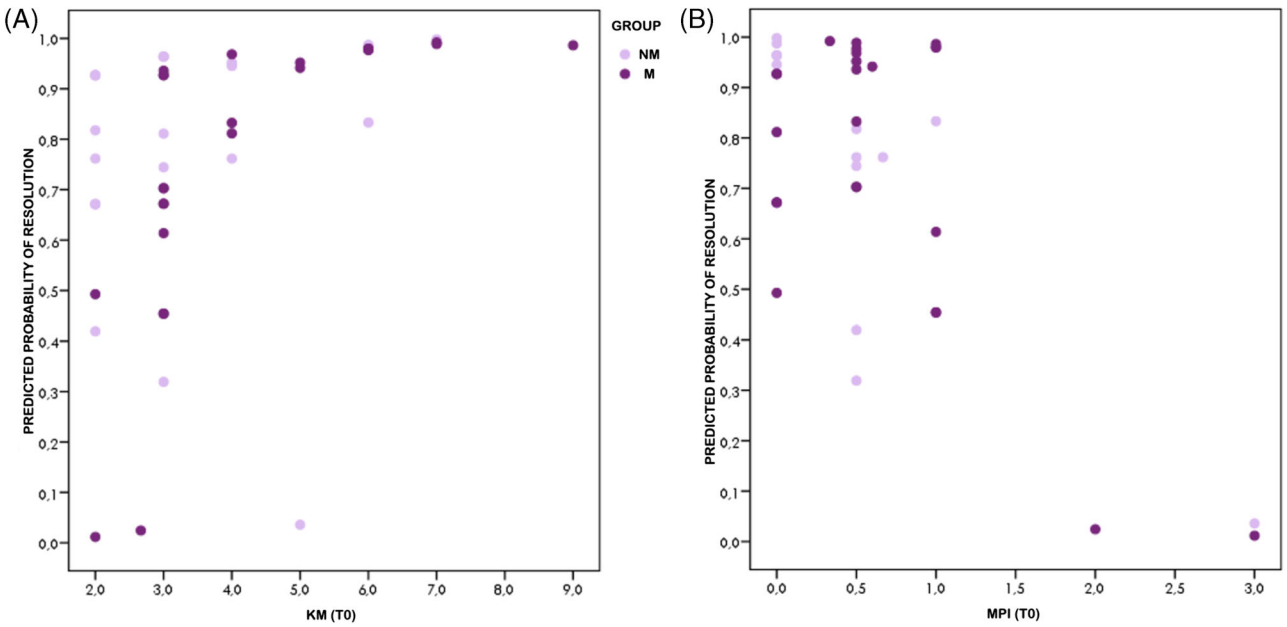

FIGURE 3 Impact of (**A**) KM width and (**B**) mPI at T_0 on the probability of disease resolution at T_2 stratified by study groups (M and NM). KM, keratinized mucosa; M, test group; mPI, modified plaque index; NM, control group

strategies, has been advocated in defects exhibiting morphologic characteristics that promote containment. In fact, reconstructive therapy proved safe and effective in these scenarios.[29] Nevertheless, the dilemma on whether to use a barrier membrane in combination with the bone grafting material or not is still a subject of discussion. The present randomized clinical trial failed to prove an added clinical and radiographic value of using a barrier

TABLE 1 Description of peri-implant clinical/radiographic parameters at baseline (T_0), 6 months (T_1), and 12 months (T_2)

	Membrane			No membrane		
Variables	***n***	**Mean + SD**	***p* value**	***n***	**Mean + SD**	***p* value**
PPD (mm)						
T_0	26	6.53 ± 1.09		25	7.04 ± 1.42	
T_1	26	3.21 ± 0.53		25	2.91 ± 0.73	
T_2	24	3.13 ± 0.68		24	3.01 ± 0.72	
T_0-T_1		3.33 ± 1.21	<0.001***		4.13 ± 1.45	<0.001***
T_0-T_2		0.08 ± 0.67	1.000		0.10 ± 0.51	0.819
T_0-T_2		3.41 ± 1.15	<0.001***		4.03 ± 1.47	<0.001***
PPDmax (mm)						
T_0	26	8.63 ± 1.53		25	8.71 ± 1.60	
T_1	26	3.88 ± 1.08		25	3.46 ± 1.02	
T_2	24	4 ± 1.18		24	3.67 ± 1.05	
T_0-T_1		4.75 ± 1.82	<0.001***		5.25 ± 1.48	<0.001***
T_0-T_2		0.13 ± 0.90	1.000		0.21 ± 0.88	0.705
T_0-T_2		4.63 ± 1.79	<0.001***		5.04 ± 1.76	<0.001***
mSBI						
T_0	26	1.63 ± 0.83		25	1.64 ± 0.80	
T_1	26	0.05 ± 0.08		25	0.07 ± 0.12	
T_2	24	0.13 ± 0.20		24	0.15 ± 0.25	
T_0-T_1		1.58 ± 0.88	<0.001***		1.57 ± 0.78	<0.001***
T_0-T_2		0.08 ± 0.18	0.058		0.08 ± 0.18	0.045*
T_0-T_2		1.50 ± 0.85	<0.001***		1.49 ± 0.79	<0.001***
SUP						
T_0	26	0.57 ± 0.68		25	0.60 ± 0.59	
T_1	26	0 ± 0		25	0 ± 0	
T_2	24	0.01 ± 0.07		24	0.03 ± 0.17	
T_0-T_1		0.57 ± 0.68	<0.001***		0.60 ± 0.59	<0.001***
T_0-T_2		0.01 ± 0.07	0.819		0.03 ± 0.17	0.876
T_0-T_2		0.56 ± 0.66	<0.001***		0.56 ± 0.65	<0.001***
KM (mm)						
T_0	26	4.15 ± 1.82		25	3.25 ± 1.48	
T_1	26	3.04 ± 1.60		25	2.50 ± 1.64	
T_2	24	2.79 ± 1.44		24	2.04 ± 1.60	
T_0-T_1		1.11 ± 1.49	0.002**		0.75 ± 1.39	0.005**
T_0-T_2		0.25 ± 1.22	1.000		0.46 ± 0.83	0.015*
T_0-T_2		1.36 ± 2.06	0.015*		1.21 ± 1.25	<0.001***
mPI						
T_0	26	0.66 ± 0.69		25	0.34 ± 0.64	
T_1	26	0 ± 0		25	0.03 ± 0.11	
T_2	24	0.04 ± 0.10		24	0.08 ± 0.18	
T_0-T_1		0.66 ± 0.69	<0.001***		0.31 ± 0.56	0.008**
T_0-T_2		0.04 ± 0.10	0.114		0.06 ± 0.15	0.165
T_0-T_2		0.62 ± 0.69	<0.001***		0.26 ± 0.57	0.090
MR (mm)						
T_0	26	0.71 ± 0.86		25	0.42 ± 1.21	
T_1	26	1.29 ± 0.86		25	1.67 ± 1.13	

(Continues)

TABLE 1 (Continued)

Variables	Membrane			No membrane		
	n	Mean + SD	*p* value	*n*	Mean + SD	*p* value
T_2	24	1.04 ± 0.81		24	1.54 ± 0.93	
T_0-T_1		2 ± 0.98	<0.001***		2.08 ± 0.83	<0.001***
T_0-T_2		0.25 ± 0.61	0.321		0.13 ± 0.68	1.000
T_0-T_2		1.75 ± 0.94	<0.001***		1.96 ± 0.81	<0.001***
MBL (mm)						
T_0	26	4.58 ± 1.45		25	4.65 ± 1.18	
T_2	24	2.85 ± 1.61		24	2.92 ± 1.35	
T_0-T_2		1.72 ± 0.72	<0.001***		1.73 ± 0.83	<0.001***
WD (mm)						
T_0	26	2.02 ± 0.64		25	2.21 ± 0.47	
T_2	24	1.20 ± 0.96		24	1.78 ± 0.98	
T_0-T_2		0.82 ± 0.90	<0.001***		0.43 ± 0.78	<0.001***
DA (°)						
T_0	26	44.48 ± 15.48		25	42.41 ± 12.40	
T_2	24	67.18 ± 15.68		24	63.01 ± 13.16	
T_0-T_2		−22.70 ± 13.33	<0.001***		−20.61 ± 14.18	<0.001***

Note: Intragroup estimations obtained from a generalized linear model with repeated measures by generalized estimation equations. *p* values are expressed with Bonferroni's correction.

Abbreviations: DA, defect angulation; KM, keratinized mucosa; MBL, marginal bone level; mPI, modified plaque index; MR, mucosal recession; msBI, modified sulcular bleeding index; PPD, probing pocket depth; SUP, suppuration; WD, defect width.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

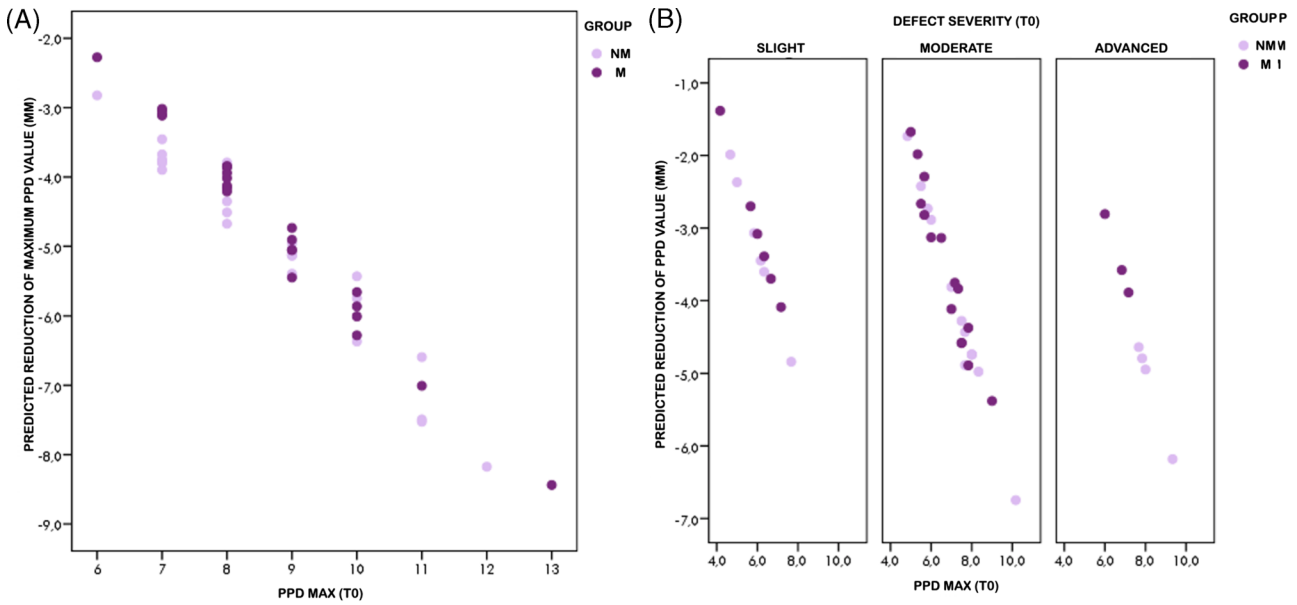

FIGURE 4 Significance of (**A**) mean PPD and peri-implant defect severity on PPD and (**B**) maximum PPD at T_0 on the predicted reduction of highest PPD value. M, test group; NM, control group; PPD, probing pocket depth

membrane in reconstructive therapy of contained bone defects. Moreover, a higher tendency to succeed in reconstructive therapy falls in sites with more effective plaque control at T_0, in sites that exhibit a wider buccal band of KM, and in women when compared to men.

4.2 | Agreements and disagreements with previous findings

Reports up to date seem to support the use of reconstructive therapy to increase the radiographic defect fill[12,13] and to limit MR after therapy.[18,30] Jepsen et al., in a

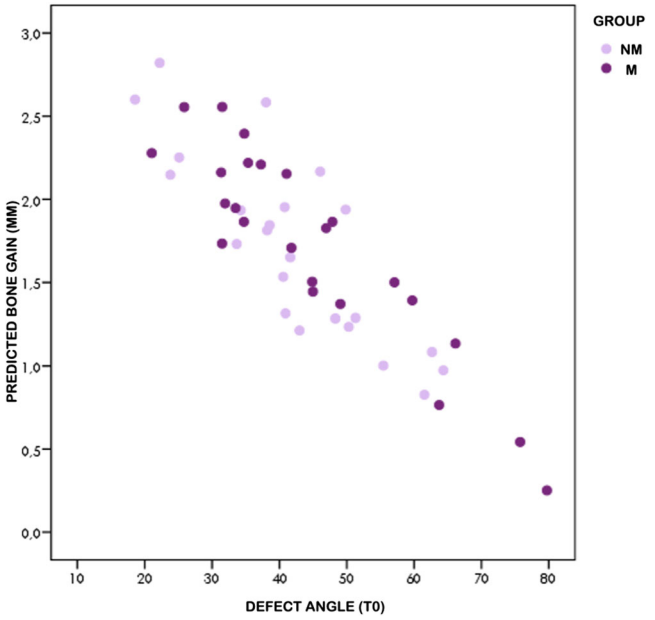

FIGURE 5 Influence of defect angulation at T_0 on marginal bone level gain at T_2 stratified by study groups. M, test group; NM, control group

multicenter randomized clinical trial, demonstrated the outperformance in terms of radiographic fill (3.6 mm) of grafting with porous titanium granules when compared to open flap debridement (1.1 mm). However, no superiority in terms of clinical parameters was yielded.[12] Renvert et al., in a 12-month randomized clinical trial, showed the added benefit in terms of increased radiographic MBL but not of clinical parameters of bone grafting combined with a barrier membrane (2.7 mm) when compared with open flap debridement (1.4 mm).[13] Hürzeler et al., in a preclinical model, validated the beneficial use of bone grafting combined with barrier membrane to enhance radiographic MBL.[17] This approach has further been proven beneficial in case series and cohort studies.[31–35] Therefore, 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 5-year follow-up study, Ross-Jansåker et al. 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).[19] In contrast, Schwarz et al., in a 4-year 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.[36] In agreement, Isler et al., in a 3-year clinical trial, demonstrated the outperformance of bone grafting combined with barrier 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.[20] Our findings, however, indicate that barrier membrane does not exert an influence on the clinical and radiographic variables. In fact, radiographic bone gain was similar for both groups (1.7 mm). This might be due to the following reasons: (1) the distribution of defect configuration, and (2) the nature and stability achieved by the bone grafting material. In our study, 60% of the peri-implantitis bone defects exhibiting 3-/4-wall morphology and the remaining 40% showed a supracrestal component in combination with the intraosseous defect. For instance, Isler et al. instead only excluded 1-wall bone defects.[20] In addition, implants eligible for this study had to be inside the bony housing in contrast to others that do not consider this factor. Rosen et al. noticed that, regardless of bone defect configuration, implants outside the bony envelope are less prone to display favorable outcomes by means of reconstructive therapy.[24] Moreover, another critical aspect that may help in interpreting the outcomes is the nature of the biomaterial. While previous studies only used particulated bone, a mixture of particulated mineralized and fibered demineralized materials was applied. The demineralized fibers interlock, allowing the graft to become moldable upon hydration to conform the surgical site. This provides the particulated graft with more stability and may promote space maintenance. Besides, the preservation process of the demineralized allograft exposes natural growth factors leading to an enhanced osteoblast activity and proliferation.[37] In agreement, Wen et al. reported radiographic and clinical outcomes comparable to ours using a mixture containing demineralized allograft and barrier membrane in a nonsubmerged healing approach.[14]

It is interesting to highlight from our findings that three variables assessed showed being significant in the resolution of peri-implantitis. Lower mPI at T_0 was statistically associated with a higher tendency in disease resolution. Lagervall and Jansson showed that the success rate in managing peri-implantitis was significantly lower for individuals with poor oral hygiene (OR = 2.9).[38] Monje et al. demonstrated that unresolved peri-implantitis after reconstructive therapy tended to display 18.3% higher mPI compared to resolved sites.[31] It is key to understand that peri-implantitis is driven by an inflammatory response to a bacterial insult. Therefore, it is discouraged to apply therapeutic measures in patients that did not respond favorably to the motivational/educational phase.[39,40] Moreover, the GEE model yielded significance for KM. In fact, every additional 1 mm of KM increases de odds for resolution up to 110% (OR = 2.1). Recently, the DGI/SEPA/Osteology Workshop suggested that "a reduced width of KM is associated with increased biofilm accumulation, soft-tissue inflammation, greater patient discomfort, mucosal recession, marginal bone loss and an increased prevalence

of peri-implantitis."[41] A plethora of studies have certainly identified the role of KM on peri-implant tissue stability.[42–44] Limited data, however, exist on the association of KM on the therapeutic outcomes of peri-implantitis. Ravidà et al. failed to link KM and disease resolution.[45] On the other hand, Monje et al. demonstrated that a wide band of KM significantly favors disease resolution in resective therapy (OR = 5.9).[15] In agreement with the latter, our findings indicate that the wider the band of KM, the higher the likelihood of disease resolution. This finding might be due to the enhanced patient comfort during postoperative brushing or to a lesser proinflammatory response, as suggested in clinical studies.[46,47] It must be considered that, according to our findings, the band of KM tended to narrow down to 1.2 mm. This implies that if it is desired to have a minimum of 2 mm after therapy to maintain health, >3 mm at T_0 might be needed. This must be further explored in future studies as suggested previously elsewhere.[48] Last but not least, defects resolved five times more frequently in women compared to peri-implantitis in men (OR = 5.5). This is not surprising as "spontaneous" oral hygiene behavior demonstrated being more efficient in women than in men.[49]

4.3 | Limitations and recommendations for future research

It is relevant to note that all the patients who completed the study followed strict adherence to supportive therapy. It is unlikely to achieve such outcomes in noncompliers to supportive measures.[48] Hence, only patients completely motivated are eligible for this therapeutic strategy. Into the bargain, it must be disclosed that these reconstructive approaches were not compared with nonreconstructive strategies (i.e., open flap debridement) to test the effect of grafting upon the clinical and radiographic outcomes. Therefore, this must be further explored in studies with longer follow-up. Moreover, findings obtained from this study are applicable to contained defects in implants placed within the bony housing. Thus, the expendability of barrier membrane might not be suitable in defects that that are less contained due to inadequate buccolingual implant position.[24] Last but not least, probe selection and its features (including tip diameter) may also lead to force differences in probing. Hence, this should be homogenized in future studies to minimize measurement errors.[50]

5 | CONCLUSION

Reconstructive therapy by means of a mixture of mineralized and demineralized allografts is effective in clinically resolving peri-implantitis and in gaining radiographic bone level. The addition of a barrier membrane to reconstructive therapy of peri-implantitis does not seem to enhance the outcomes of contained bone defects.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the conception and design of the study. Alberto Monje has been involved in data collection, conception, design of this study, and drafting the manuscript. Ramón Pons and Javi Vilarrasa have been involved in data analysis and data interpretation. José Nart and Hom-Lay Wang have been involved in the critical review of the manuscript and have given final approval of the version to be published.

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CONFLICT OF INTEREST

The authors have no direct financial interests with the products and instruments listed in this paper.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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