Significance of Barrier Membrane on the Reconstructive Therapy of Peri-Implantitis: A Randomized Controlled Trial

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All authors have made substantial contributions to conception and design of the study. AM has been involved in data collection, conception, design of this study and drafting the manuscript. RP and JV have been involved in data analysis and data interpretation. JN and HLW have been involved in the critical review of the manuscript and have given final approval of the version to be published.

Abstract

Objective: 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 criteria for disease resolution was defined a priori. A generalized linear model (GLM) of repeated measures with generalized estimation equations (GEE) statistical methods were used.

Results: Overall, 33 patients ($n_{implants}$=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 (OR=1.55, p=0.737). Conversely, the odds of disease resolution were statistically associated with modified plaque index (mPI) recorded at T_0 (OR=0.13, p=0.006) and keratinized mucosa (KM) 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).

MeSH keywords: dental implants, peri-implantitis, regeneration, wound healing, biocompatible materials, jaw

Introduction

Peri-implantitis represents a biofilm-mediated inflammatory condition that courses with progressive bone loss.[1] This entity may compromise the longevity of dental implants, thus impacting negatively on the quality of life of patients. On the top of that, 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 manoeuvres to establish a healthy ecosystem and to minimize the risk of recolonization.[5] Implant removal indeed is the most predictable strategy to resolve the condition, nevertheless, it may not satisfy the patients´ demands concerning function, chewing, aesthetics and phonetics.[6] On the other side, the therapy 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. Non-surgical measures have shown unsatisfactory in terms of disease resolution.[8] Surgical strategies, on the other side, 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 the 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] combined defects exhibiting supra-crestal 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, Renvert et al. in a 12-month randomized clinical trial 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. challenged this finding as no marked differences, but in mucosal recession, were yielded when compared reconstructive therapy only by means of bone grafting when compared 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, Isler et al. in a 3-year clinical trial 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.

Material 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 CICOM-MONJE Institute (Badajoz, Spain). Patients received and signed a written inform consent. Patient data was anonymized. The study was registered and approved by www.clinicaltrials.gov (NCT05282667). The study is reported according to the CONSORT statement.[21]

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 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 in age of 18 to 80, non-smokers, 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 partial/complete edentulous patients that had no active periodontal disease. Moreover, peri-implantitis bone

defects where reconstructive therapy was indicated due to contained defect configuration combined or not with supra-crestal 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. Uncontained defects (i.e., supra-crestal bone defects -type II - or implants outside of the bony envelope – type Ia or IIIa)[23] where reconstructive therapy was not indicated, sites with <2mm of keratinized mucosa at the buccal aspect or implants outside of the bony housing based upon intra-operative visualization[24] were excluded.

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 1-4, 5-9 were included in test group, and control group, respectively. When reached the total sample size of any of the groups, patients were only recruited for the remaining groups to complete the total sample size.

Case definition of peri-implantitis

Peri-implantitis was defined according to the 2017 Word Workshop of Periodontal and Peri-implant diseases.[25] Hence, the case definition applied was as follows: presence of bleeding and/or suppuration on gentle probing (~0.2N), probing pocket depths 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 unsuitable access, the prosthesis was retrieved for accurate diagnosis.

Clinical assessment

The following clinical parameters and indices were recorded at T_0 (5-6 weeks after non-surgical therapy), 6 months and at 12-months by one previously calibrated (intra-operative k-value >85% based on a previous examination of 15% of the overall sample) examiner (AM):

- Probing pocket depth (PPD) recorded in millimeter using a plastic/metal North Carolina Probe applying an approximate probing force of 0.2N.[13]

- Modified sulcular bleeding index (mSBI) that scored 0-3 according to the extensiveness and severity of bleeding on probing (BOP).[26]
- Modified plaque index (mPI) that score 0-3 according to the visibility and severity of plaque accumulation.[26]
- Mucosal recession (MR) was defined as the distance in mm from the implant-abutment connection as a steady mark and the mucosal margin
- Keratinized mucosa (KM) around dental implants, measured from free mucosal margin to mucogingival junction at mid-buccal position, to the nearest millimeter using a North Carolina Probe.
- Suppuration (SUP) index around implants applied according to the grade of SUP: grade 0 = no SUP or non-suppurative exudate; grade 1=SUP manifesting ≥15 seconds after gentle probing or SUP at a single spot (dot); grade 2 = SUP manifesting <15 seconds 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]
- Infra-osseous component (IC) was measures intra-operatively 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.

Definition of disease resolution

Successful treatment was evaluated at the latest evaluation. Peri-implantitis was considered "resolved" if the following case definition was:

- Lack or 1 spot (not profuse) of bleeding and/or suppuration on gentle probing (~0.2N)
- Probing pocket depths of ≤5mm
- No radiographic progressive bone loss within the standard error ≥ 1mm [28]

Radiographic assessment

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

- 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 peri-apical radiograph, corrected according to the known implant pitch.
- Intra-bony defect width (WD): distance (mm) between the distal and mesial interproximal bone crest and the implant surface.
- Angulation of the intra-bony defect (DA): angle resulted from a vertical line along the outer implant surface and a line extending along the peri-implant bone defect.

Peri-implantitis bone defect morphology and severity

Characterization of the peri-implantitis defects was based on defect morphology (Classes I-III) and severity (grades S-M-A), as proposed elsewhere.[23] Briefly, according to the morphology was classified as follows: Class I: infra-osseous defect Class Ib: 2-to 3-wall 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, implants were graded as: Slight (S): <25% of the implant length, moderate (M): 25% to 50% of the implant length, and advanced(A): >50% of the implant length.

Non-surgical therapy phase

Oral hygiene instructions were instructed as part of the diagnostic phase. All eligible patients diagnosed with peri-implantitis underwent non-surgical therapy at least 5-6 weeks prior to the surgical reconstructive phase by one operator (AM). Briefly, ultrasonic debridement using a metal tip[4], a "mini-five" curette[5] and site-specific Gracey curettes[6] were used for scaling and debridement of the peri-implant sulcus. Further sub-mucosal air polishing was performed with

[4] #100 Universal, Hu-Friedy, Chicago, IL, ISA

[5] Hu-Friedy, Chicago, IL, USA

[6] Hu-Friedy, Chicago, IL, USA

an erythritol-powder using a special plastic tip[7]. Irrigation was profusely applied with chlorhexidine 0.12%.[8] Clinical assessment was performed to check resolution. If peri-implantitis was resolved, the patient was excluded from the study. For candidates for reconstructive therapy, healing abutments, were placed whenever possible, ≥2 weeks before the surgical reconstructive phase.

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[9], site-specific Gracey curettes[10] and NiTi brushes[11]. The surgical approach was tailored to the scenario. Implantoplasty was performed, whenever present uncontained components (supra-crestal or 1-to-2-wall defects with a tungsten carbide bur.[12] Surface decontamination was performed by means of NiTi brushes[13] for about 2-3 minutes at 600rpm followed by hydrogen peroxide (3%) for 2 minutes and irrigation with saline. The infra-osseous compartments were grafted using a demineralized (fibers) and mineralized (particulated) cortical allograft[14] up to the adjacent bony peaks. The test group (M group) received a cross-linked collagen membrane[15] on the top of the stratified grafting material, while the control group (NM group) no membrane was used and the demineralized fibers were left on contact with the soft tissues (Figure 2). Nylon 5.0[16] was used for suturing. All the sites were left for transmucosal (non-submerged) healing.

Post-operative care

[7] Air-Flow, EMS, Herrliberg, CH

[8] Perioaid, Dentaid, Barcelona, Spain

[9] Hu-Friedy, Chicago, IL, USA

[10] Hu-Friedy, Chicago, IL, USA

[11] Hans Korea Co., Gyenonggi-do, Korea

[12] Meisinger LLC, Nauss, Germany

[13] Hans Korea Co., Gyenonggi-do, Korea

[14] LifeNet Health, Virginia, USA

[15] RTM, Osteogenics Biomedical, Lubbock, TX, USA

[16] Resorba® Sutures, Osteogenics Biomedical, Lubbock, TX, USA

Patients were prescribed to apply 3 times a day chlorhexidine and chitosan gel in the area for 2 weeks[17], and systemic amoxicillin 750mg 2 tablets a day for 7 days was also prescribed. Moreover, anti-inflammatory medication (Ibuprofen, 600mg, 1table every 5-6 hours for 5 days) was prescribed. In 2-3 weeks, the sutures were removed, and oral hygiene resumed. At this stage, the dental hygienists performed full-mouth supra-mucosal supportive measures using the air polisher.[18] Prostheses were placed on the implants ≥4 weeks after the surgical intervention.

Recall program

During the first 2 months, patients were appointed on a 2/3-week basis after suture removal for professional-administered oral hygiene measures in the grafted area. 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-/4-month recall peri-implant maintenance therapy program supervised by the principal investigator during the first year after surgery (T_F).

Statistical analysis

Absolute and relative frequencies and means and standard deviation (SD) were used to describe the categorical and continuous variables, respectively. The homogeneous distribution of variables between study groups was analyzed through Pearson Chi^2 and Mann-Whitney test. A generalized linear model (GLM) of repeated measures with generalized estimation equations (GEE) were performed to contrast intra-group 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^2 statistic. A multiple model was further constructed to adjust the results for all the relevant

[17] Bexident Post, Isdin, Barcelona, Spain

[18] Air-Flow, EMS, Herrliberg, CH

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, suppuration, KM width, mPI, MR, DW and DA. The analysis was performed with SPSS 15.0 (SPPS Inc., Chicago, IL). The significance level used was 5% (a=0.05).

Results

Study population

The flowchart of the study is illustrated in Figure 1. From the 104 patients that were screened for eligibility, 64 did not meet the inclusion criteria and 4 did not need surgical therapy due to earlier disease resolution by means of non-surgical 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.

Demographics

The description of the main patient and implant variables is summarized in Table S1 (see online Journal of Periodontology). 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).

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. 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 3). 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, 1 additional score recorded at mPI recorded at T_0 reduced to 87% the overall probability of disease resolution, while 1 additional mm recorded at T_0 KM width increased up to 110% the chances of disease resolution (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 mm 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 (β= 0.21, p=0.292) (Table 3). 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 (β=-0.93, p<0.001) and to the severity of the radiographic bone defect (p=0.039). Particularly, 1 additional mm in the 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 (β=-1.01, p=0.031) (Figure 4).

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 mm 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 on MBL gain was negligible (β= 0.07, p=0.774) (see table S2 online Journal of Periodontology). Interestingly, peri-implant DA at T_0 was the only variable linked with greater MBL gain at T_2 (β= -0.03, p=0.001) (Figure 5). In detail, 1 positive grade (°) recorded at T_0, DA was associated to 0.03mm less MBL gain at T_2 (see table S3 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 (β=-0.01, p=0.960), SUP (β=0.01, p=0.974), KM width (β=-0.15, p=0.785), mPI (β= -0.37, p=0.059), MR (β=0.21, p=0.470), DW (β=0.39, p=0.155) or DA (β=-2.01, p=0.601).

Discussion

Principal findings

The leading feature that dictates the therapeutic modality of peri-implantitis is bone defect configuration. Reconstructive therapy, in contrast to resective therapeutic 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 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 wider buccal band of KM and in women when compared to men.

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 muti-center randomized clinical trial demonstrated the outperformance in terms of radiographic fill (3.6mm) of grafting with porous titanium granules when compared to open flap debridement (1.1mm). 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 (2.7mm) when compared with open flap debridement (1.4mm).[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 fulfil 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 (1.3mm) or without barrier membrane (1.1mm).[19] In contrast, Schwarz et al. in a 4-year study showed an enhancement in clinical and radiographic parameters that favoured to 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 (1.7mm) when compared to the use of anorganic bovine bone grafting combined with concentrated growth factors (1.4mm) in reconstructive therapy.[20] Our findings, however, indicate that barrier membrane does not exerts an influence on the clinical and radiographic variables. In fact, radiographic bone gain was similar for both groups (1.7mm). 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 supra-crestal component in combination with the infra-osseous 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 bone defect configuration, implants outside of 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 fibred demineralized materials were applied. The demineralized fibres interlock allowing the graft become moldable upon hydration to conform the surgical site. This provides the particulated graft 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 non-submerged 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 & 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 response favorably to the motivational/educational phase.[39, 40] Moreover, the GEE model yielded significance for KM. In fact, every additional 1mm of KM increases de odds for resolution in 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, exists 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 side, 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 later, our findings indicate that the wider the band of KM the higher is the likelihood of disease resolution. This finding might be due to the enhanced patients´ comfort during post-operative brushing or to a lesser pro-inflammatory 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 1.2mm. This implies that, if it is desired to have a minimum of 2mm after therapy to maintain health, >3mm at T_0 might be needed. This must be further explored in future studies as suggested previously elsewhere.[48] Last but not least, defects in women demonstrated to resolve 5x higher when compared to peri-implantitis managed in men (OR=5.5). This is not surprising as "spontaneous" oral hygiene behavior demonstrated being more efficient in women than in men.[49]

Limitations and recommendations for future research

It is relevant to note that all the patients that completed the study followed strict adherence to supportive therapy. It is unlikely to achieve such outcomes in non-compliers to supportive measures.[48] Hence, only patients completely motivated are eligible to this therapeutic strategy. Into the bargain, it must be disclosed that these reconstructive approaches were not compared with non-reconstructive 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 for contained defects in implants placed within the bony housing. Thus, the expendability of barrier membrane might not be suitable in defects that exhibit defects that

are less contained due to inadequate bucco-lingual 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]

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

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Figure 1. Flowchart of the study

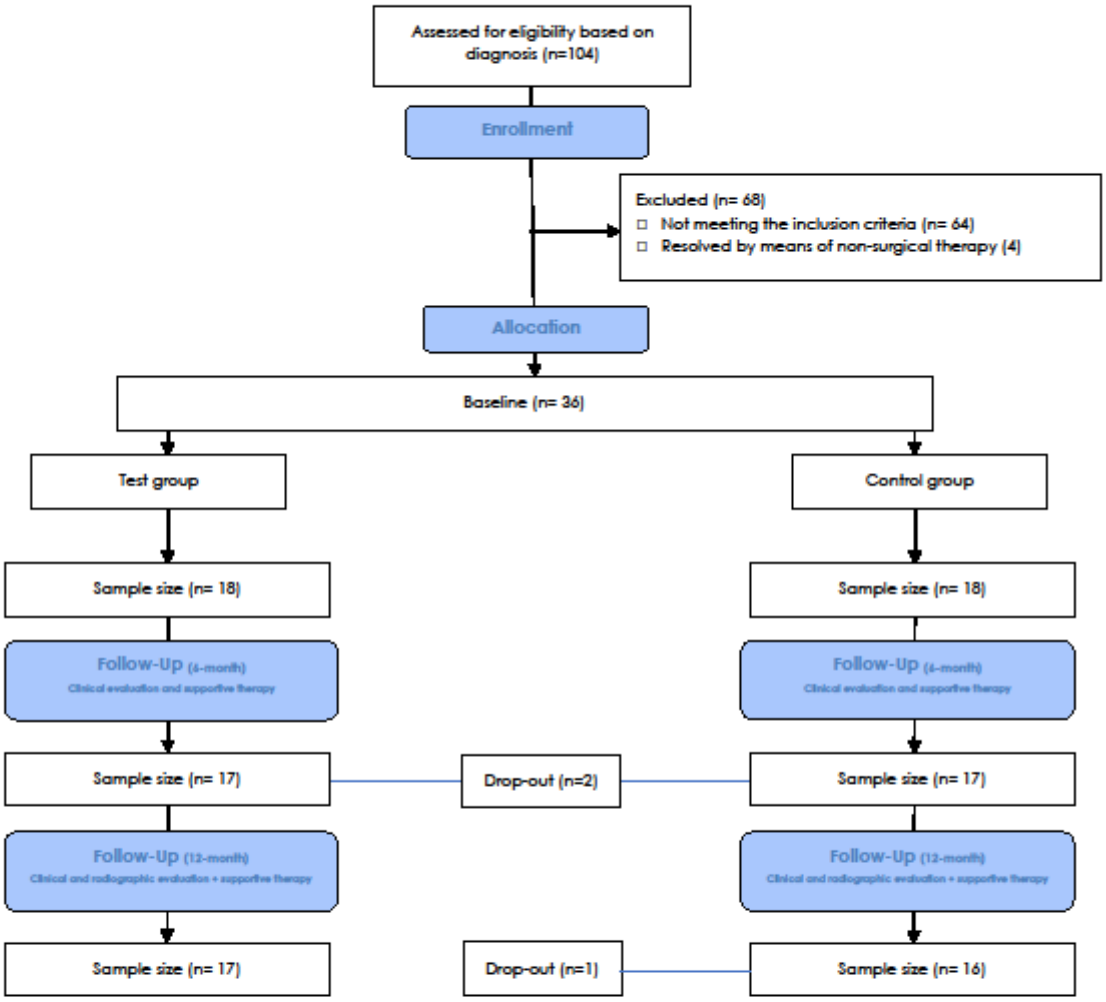
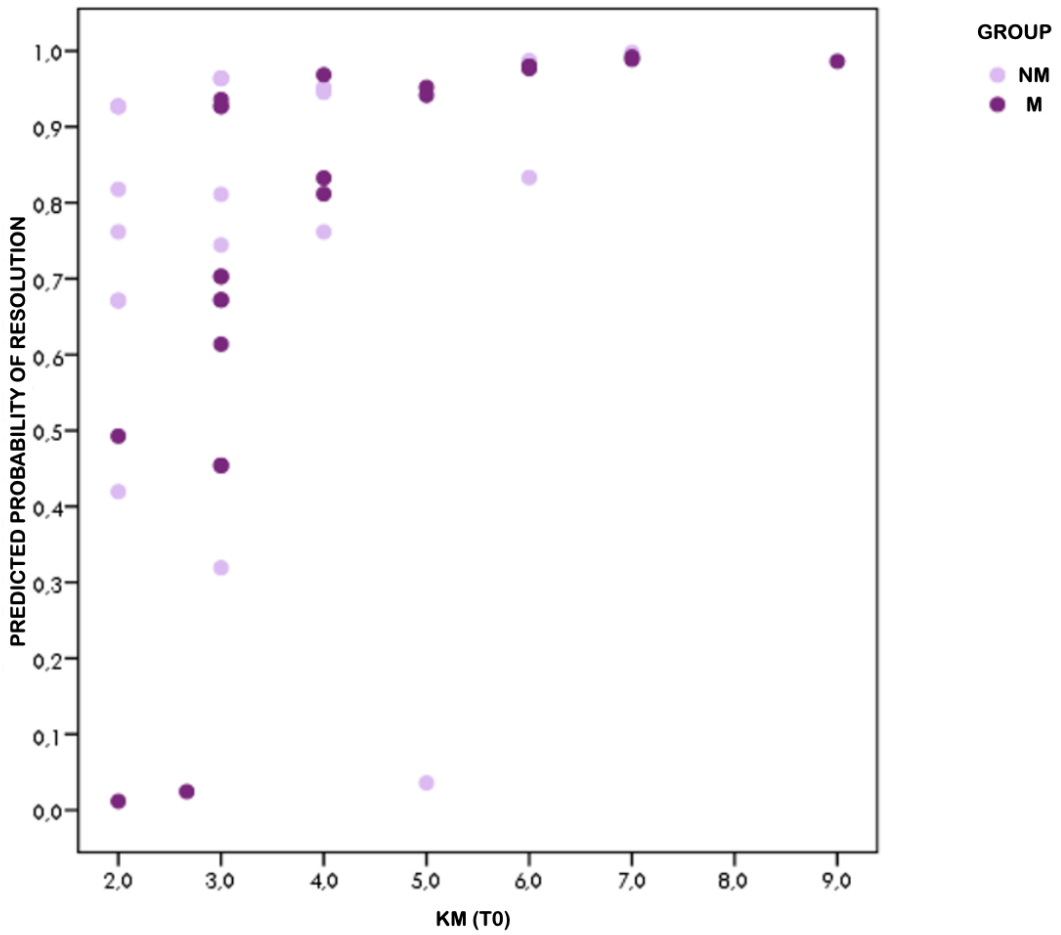
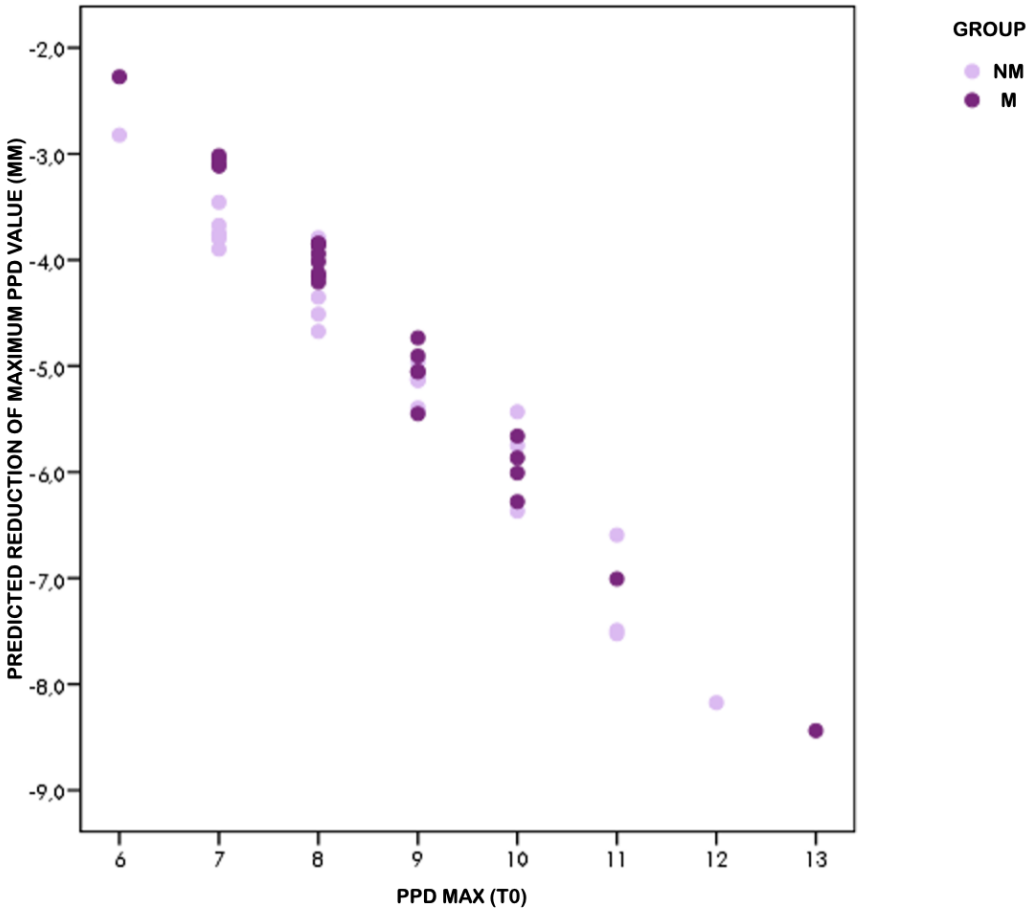
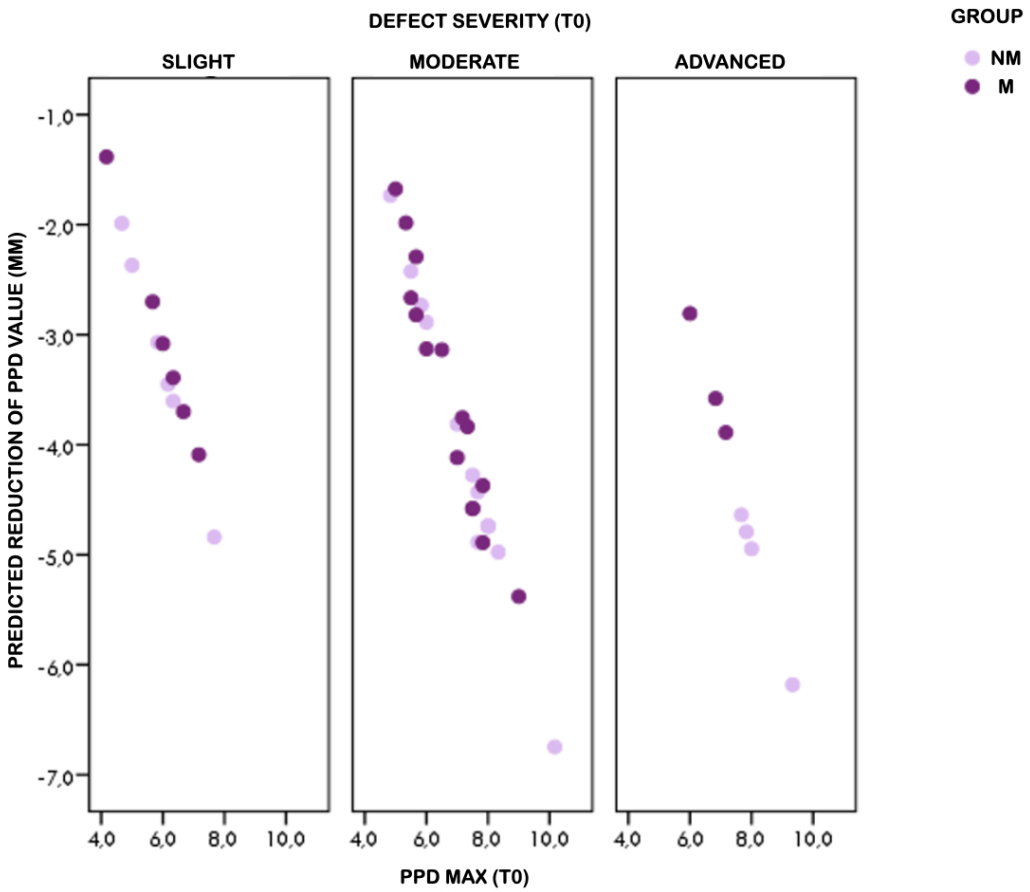


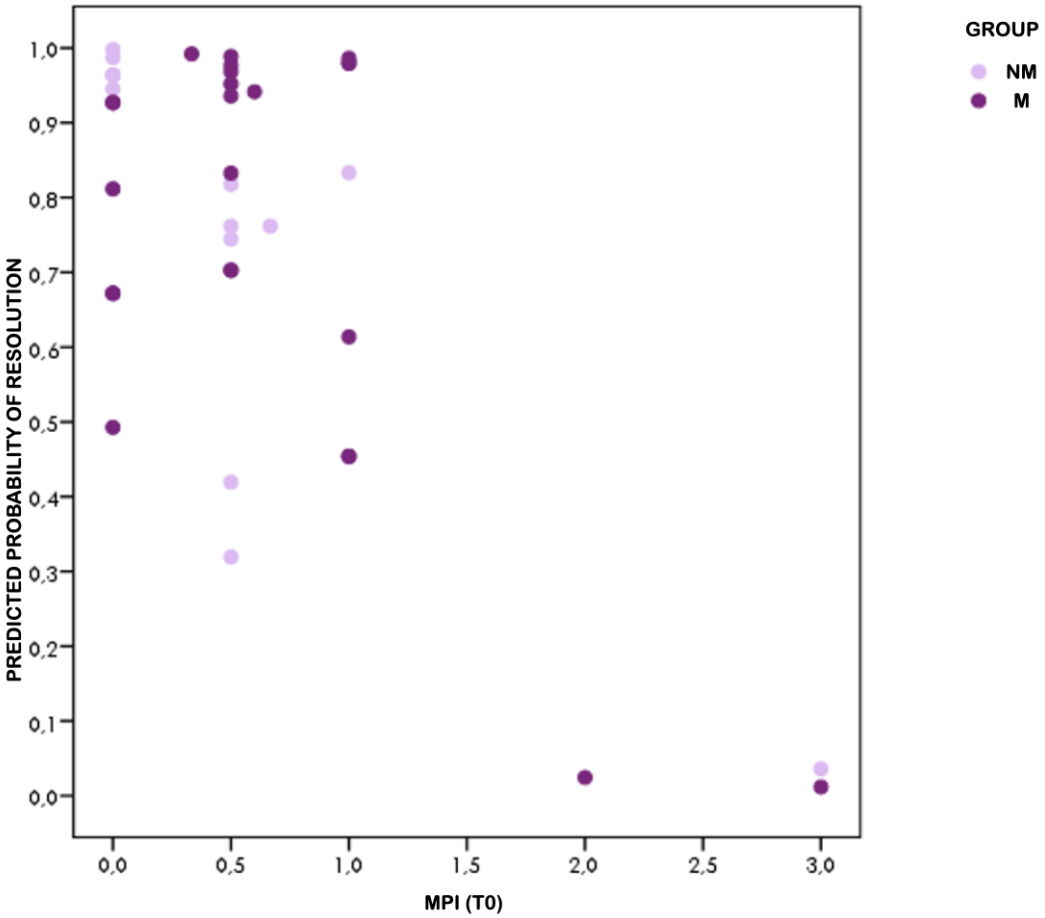
Figure 2. Case 1. Test group (M): (a-b) Initial presentation. (c)Full-thickness flap was elevated to complete the debridement of the granulation tissue and decontaminate the implant

surface. (d) Reconstructive therapy was performed by means 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. (b) Case 2. Control group (NM): (h-i) Initial presentation. (k) Full-thickness flap was elevated to complete the debridement of the granulation tissue and decontaminate the implant surface. (l) Reconstructive therapy was performed by means mineralized and demineralized allograft. (m-n) Disease resolution and MBL gain was noted at T_2









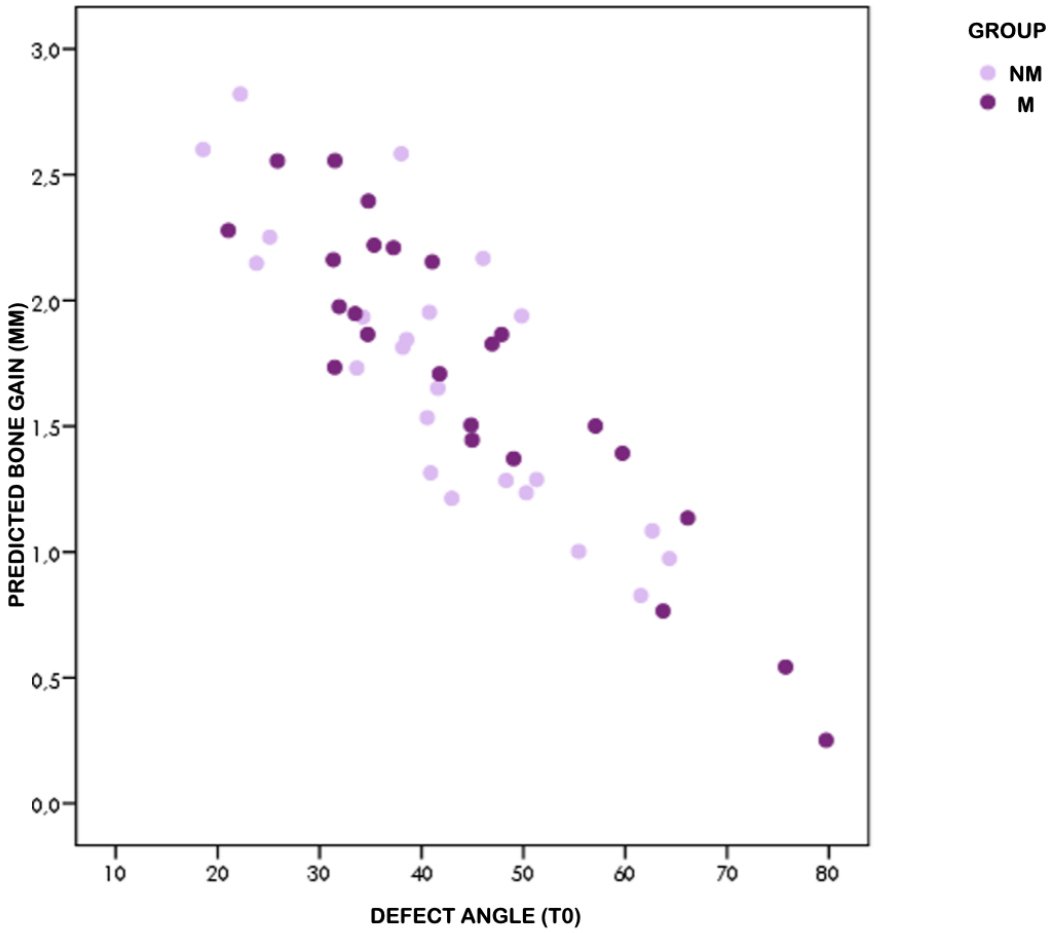
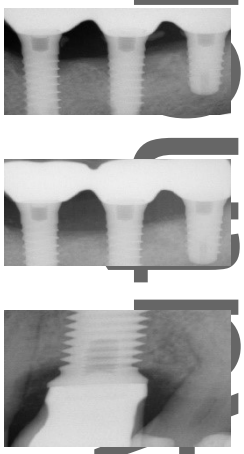


Figure 3. Impact of (A) KM width and (B) mPI at T_0 on the probability of disease resolution at T_2, stratified by study groups (M and NM)



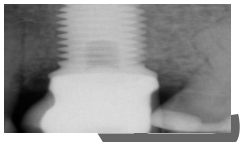
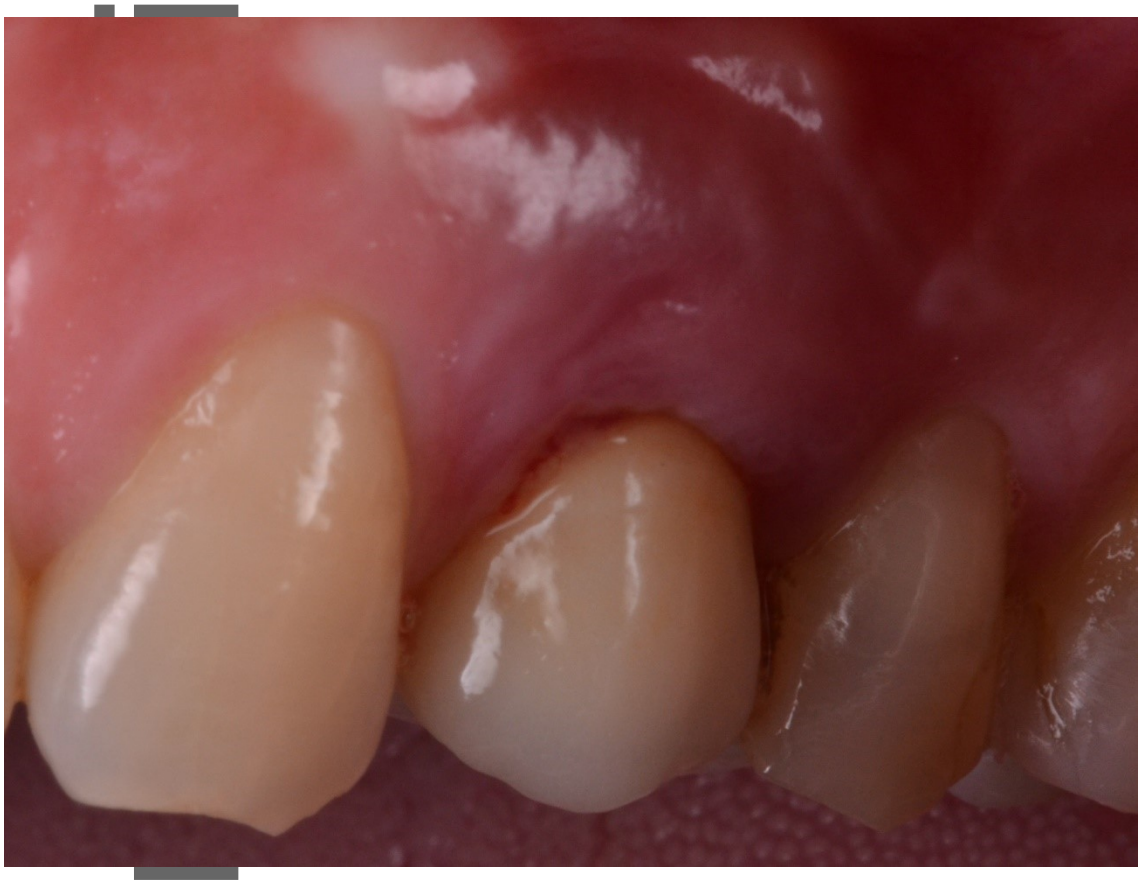
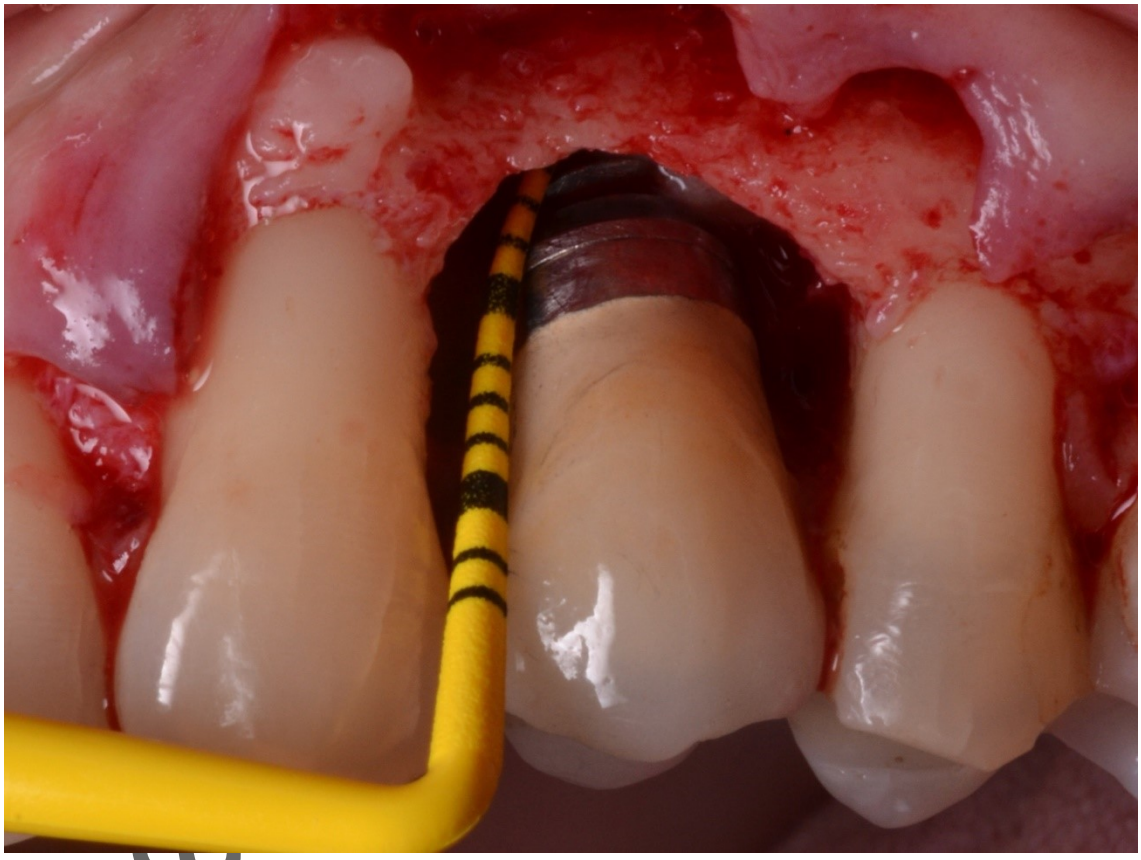
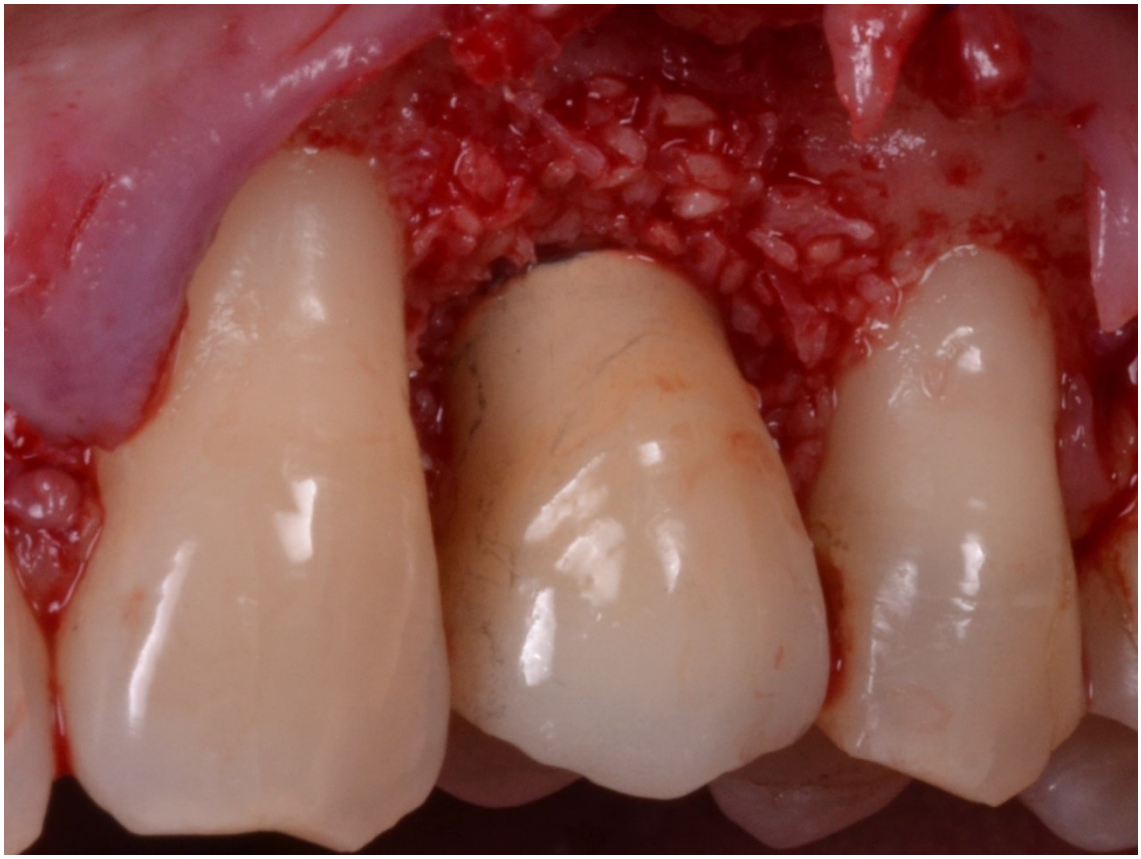
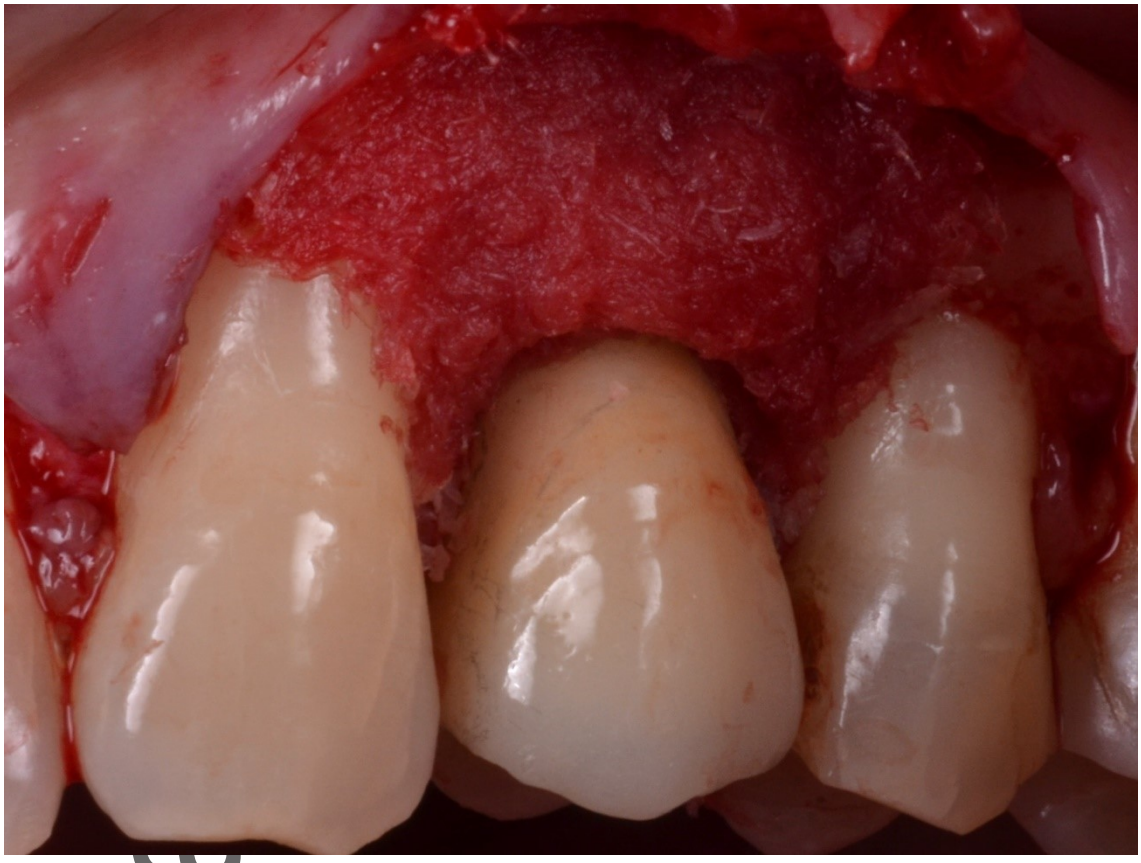


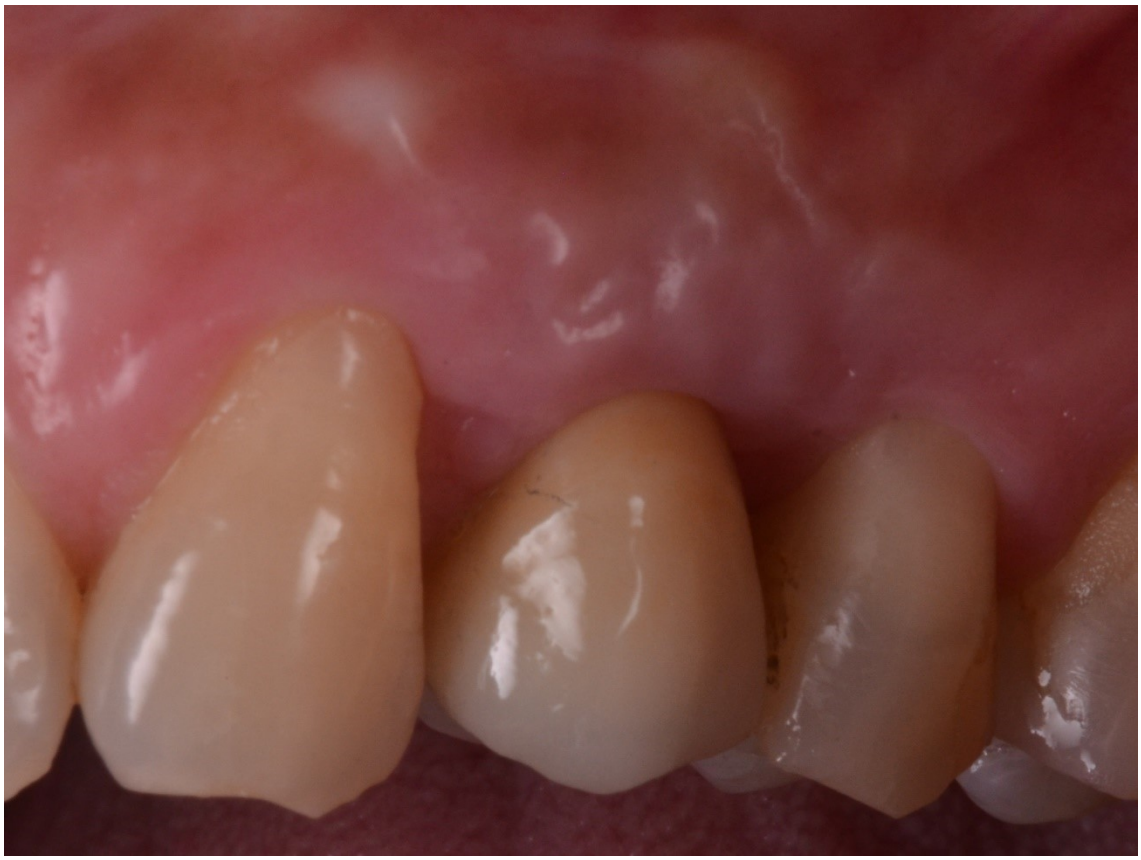
Figure 4. Significance of (a) mean PPD and peri-implant defect severity on PPD and (b) maximum PPD at T_0 on the predicted reduction of highest PPD value

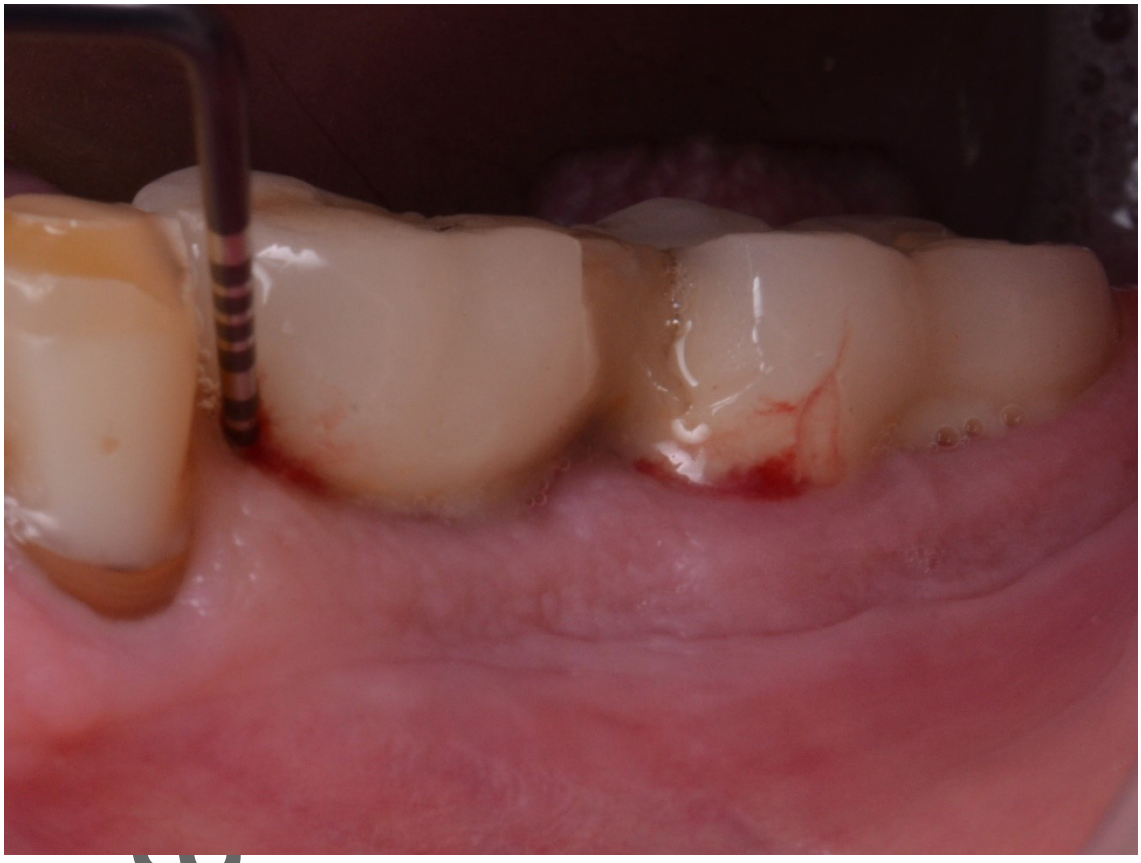


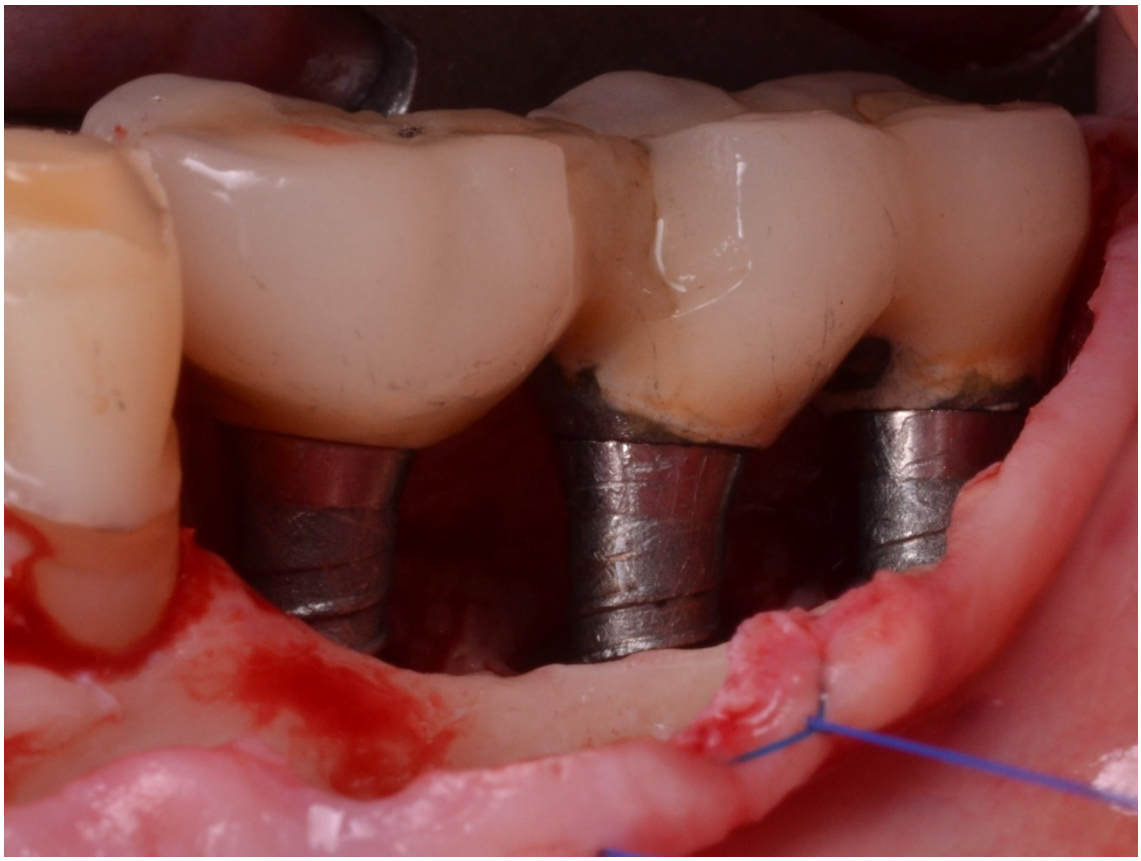


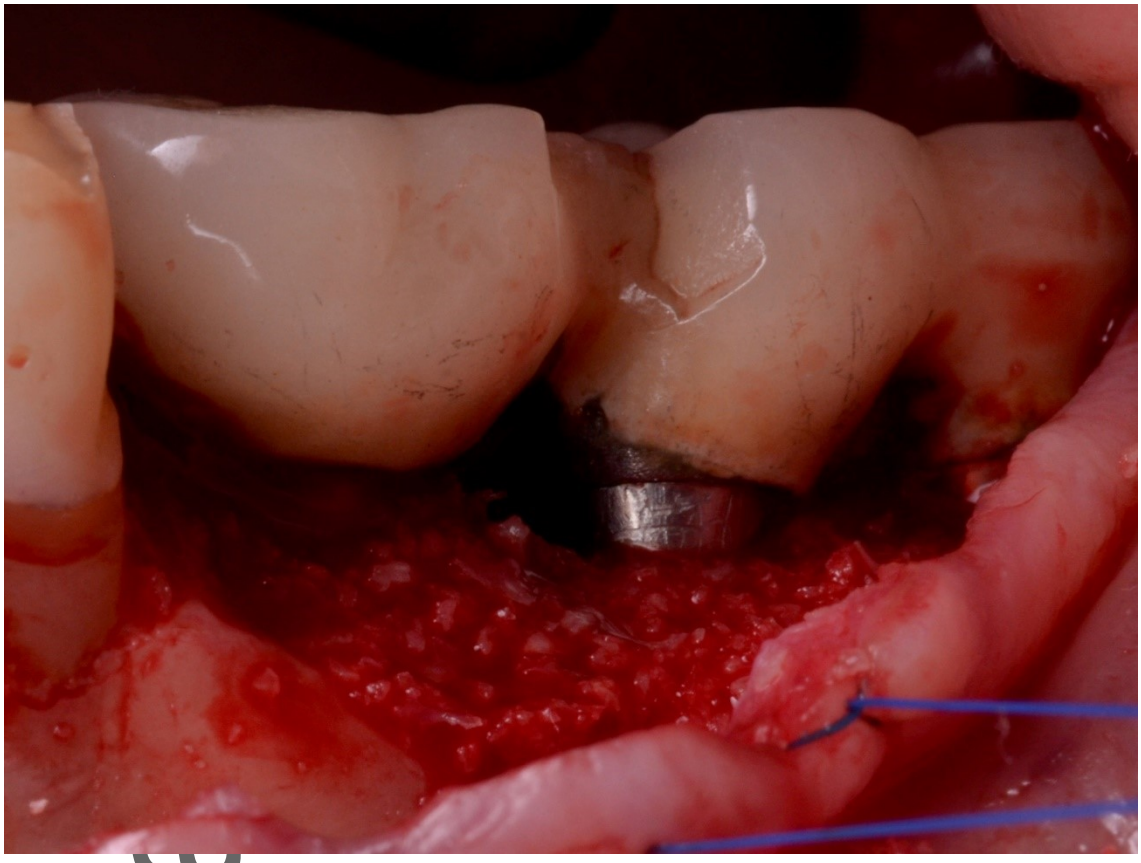


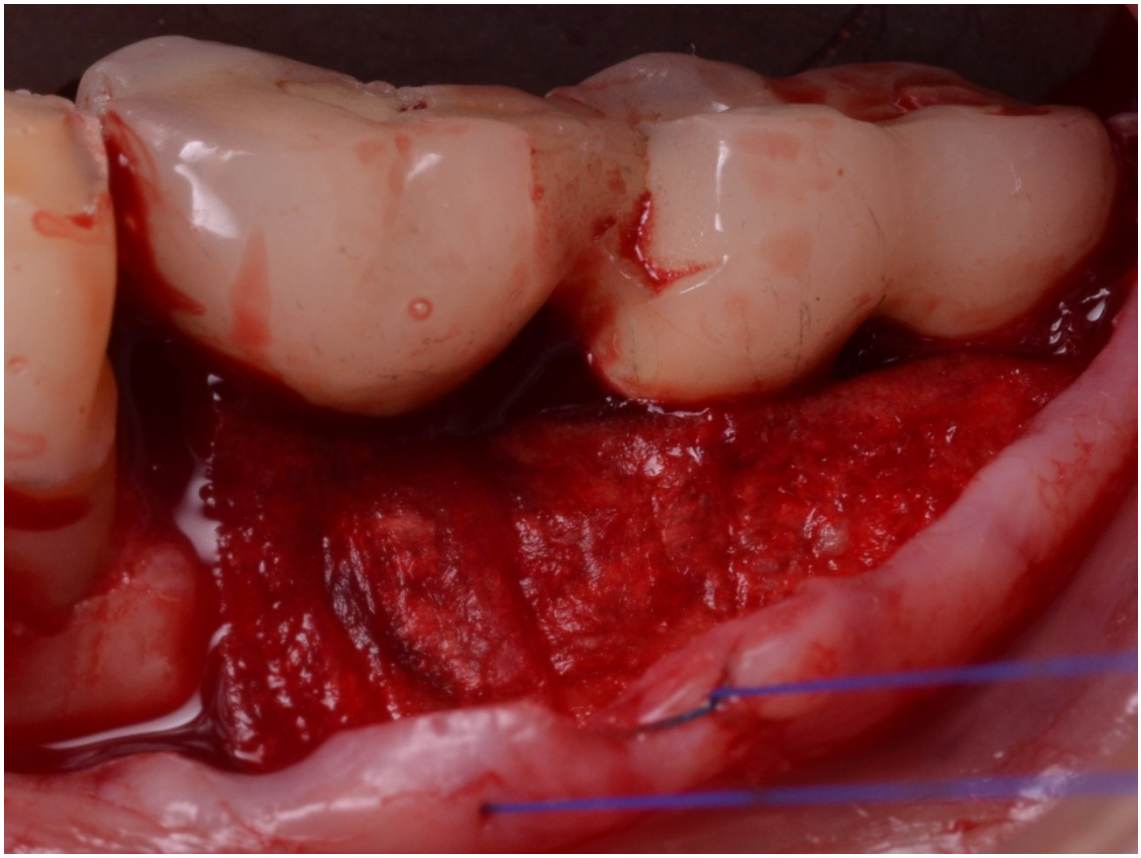












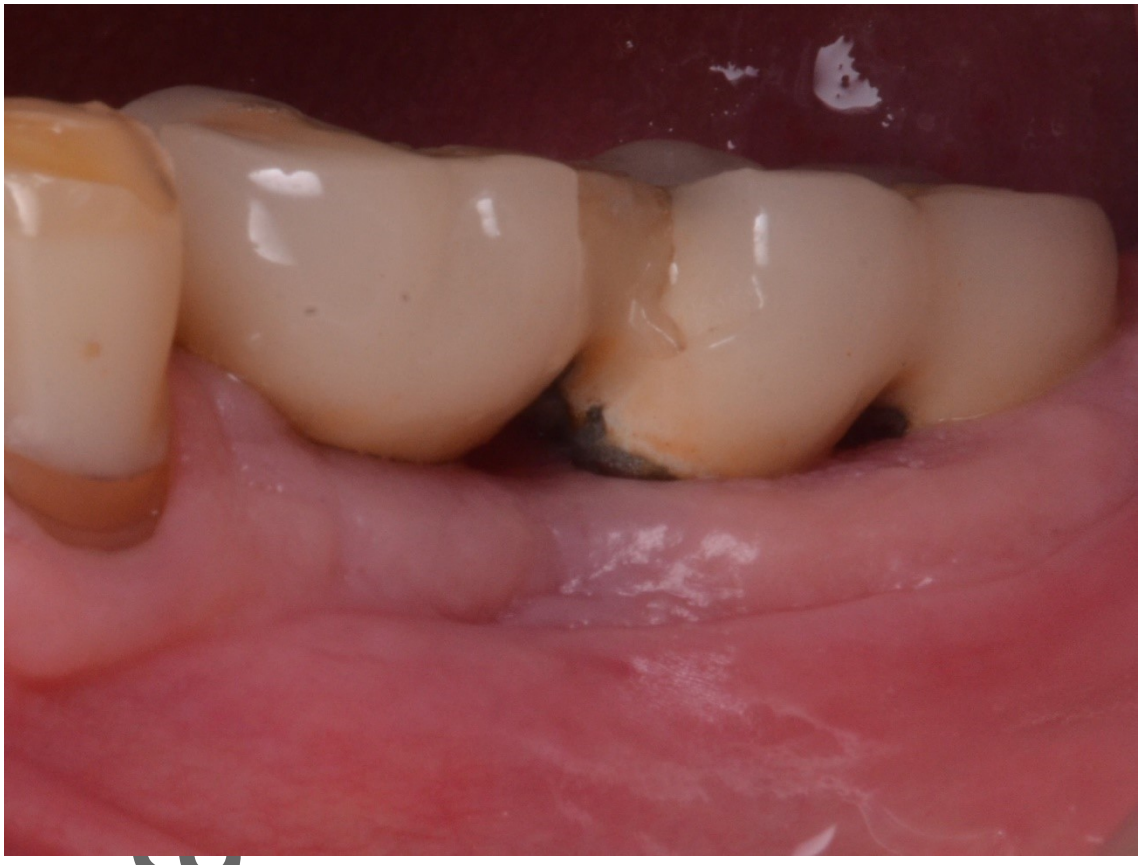
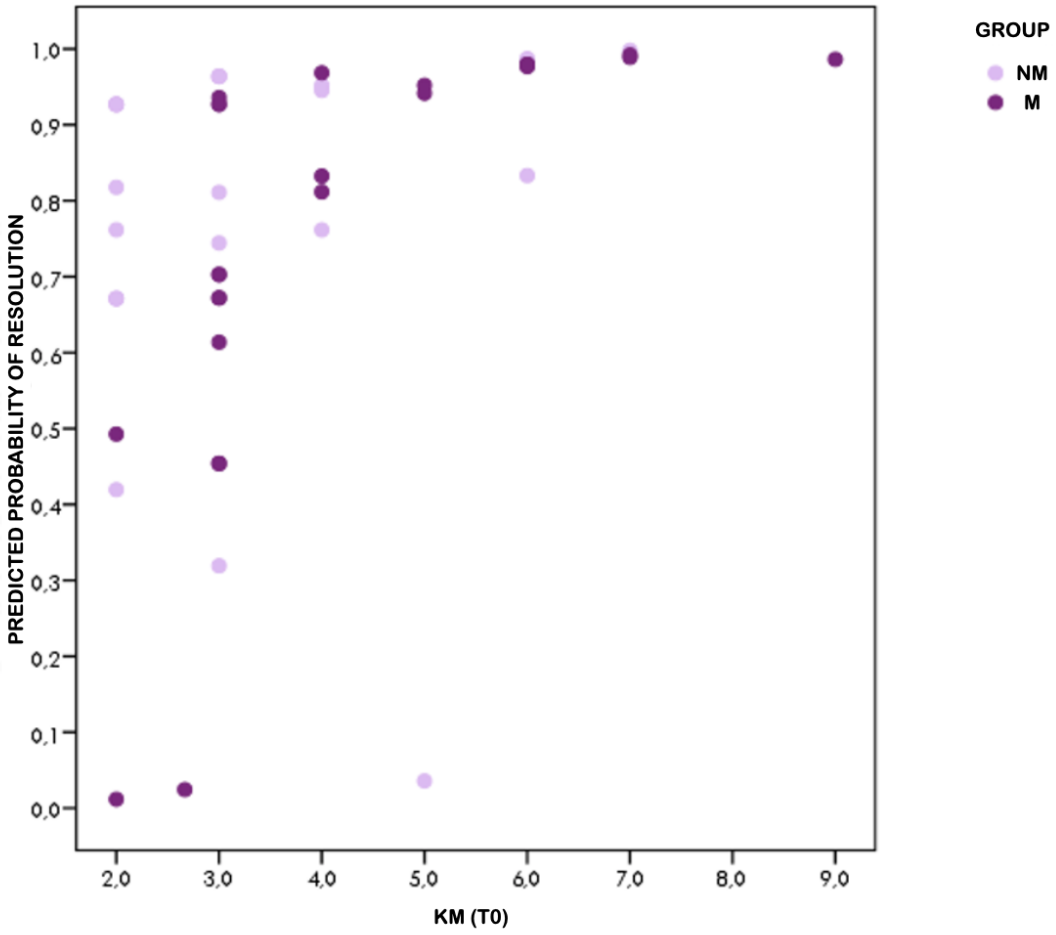
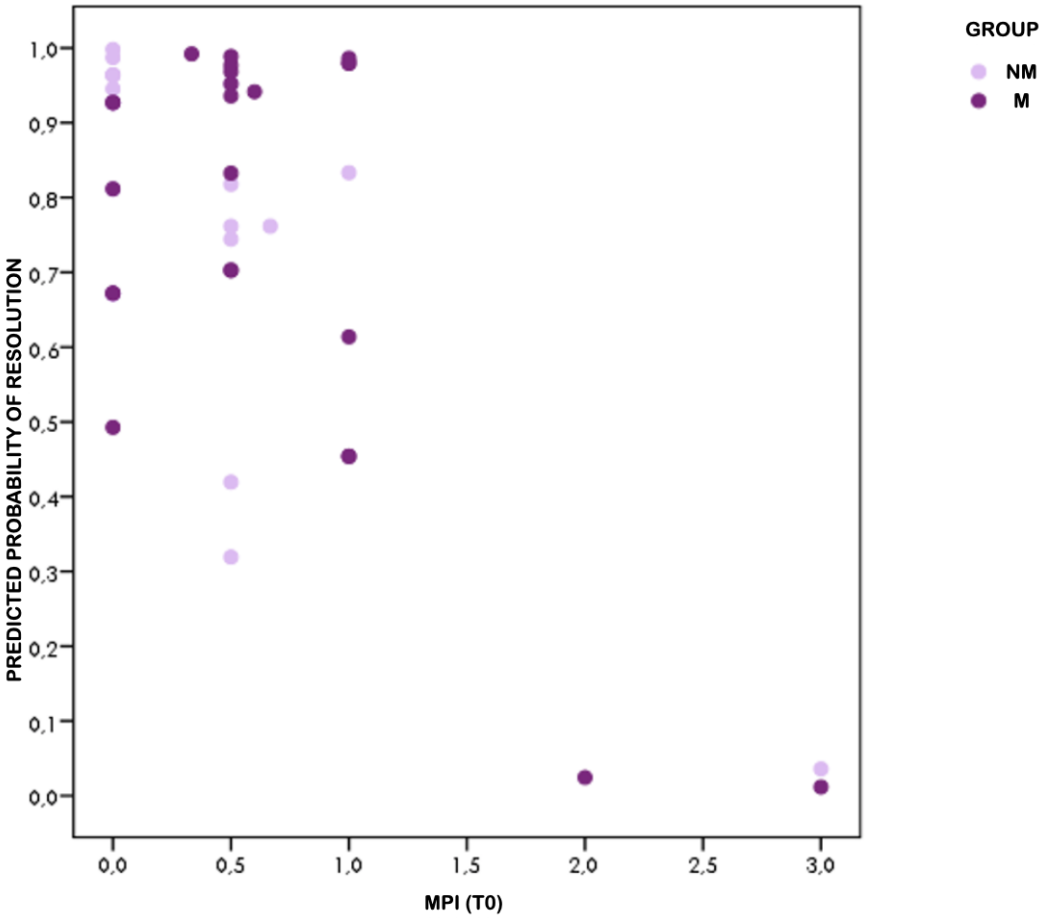
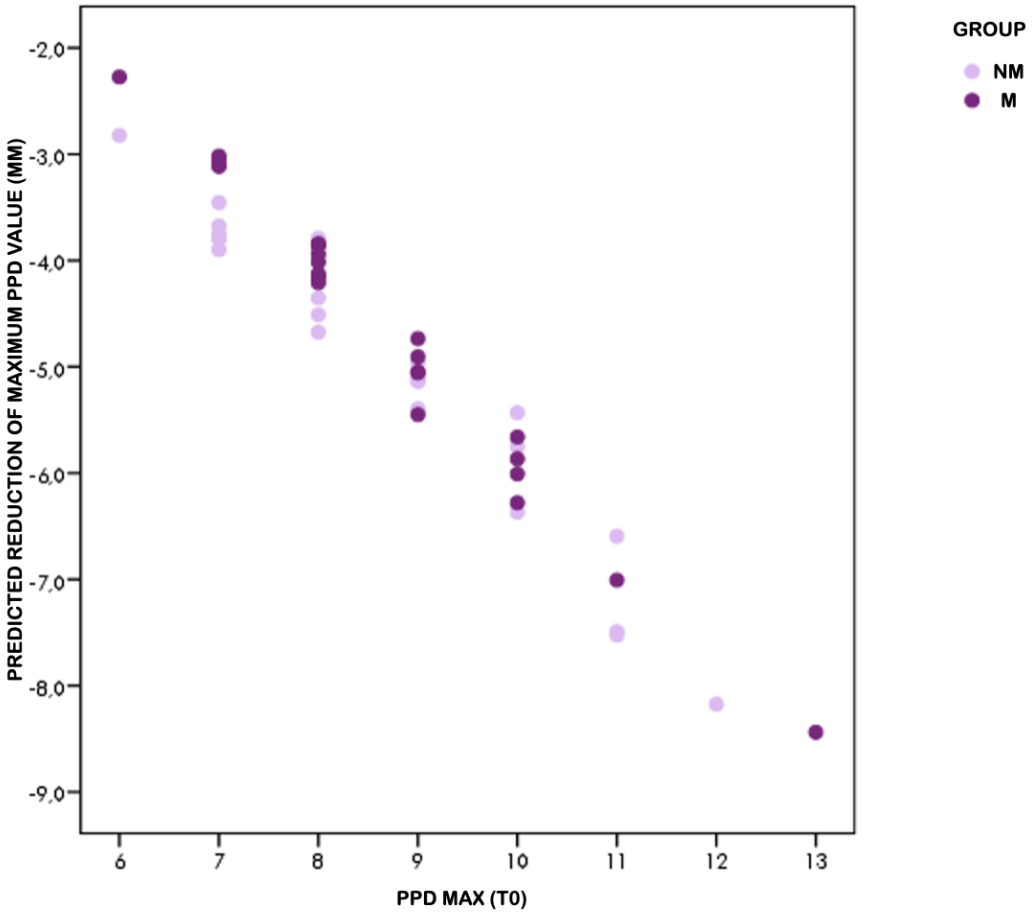
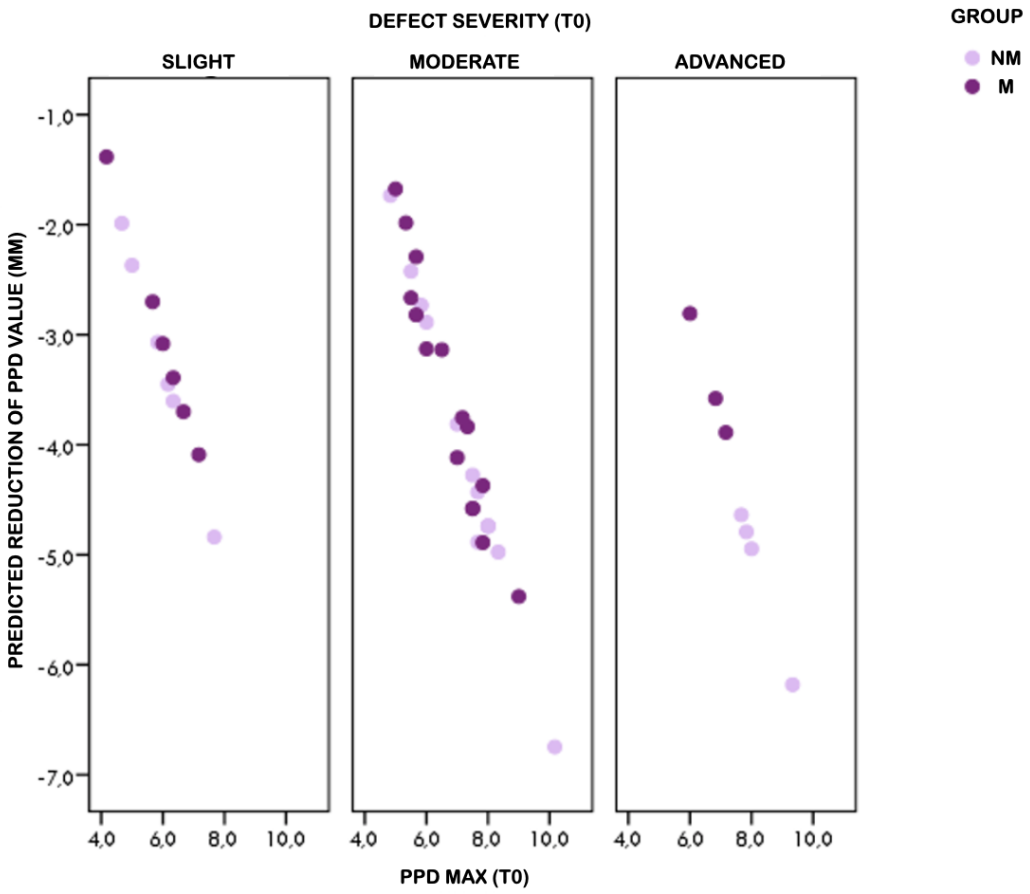


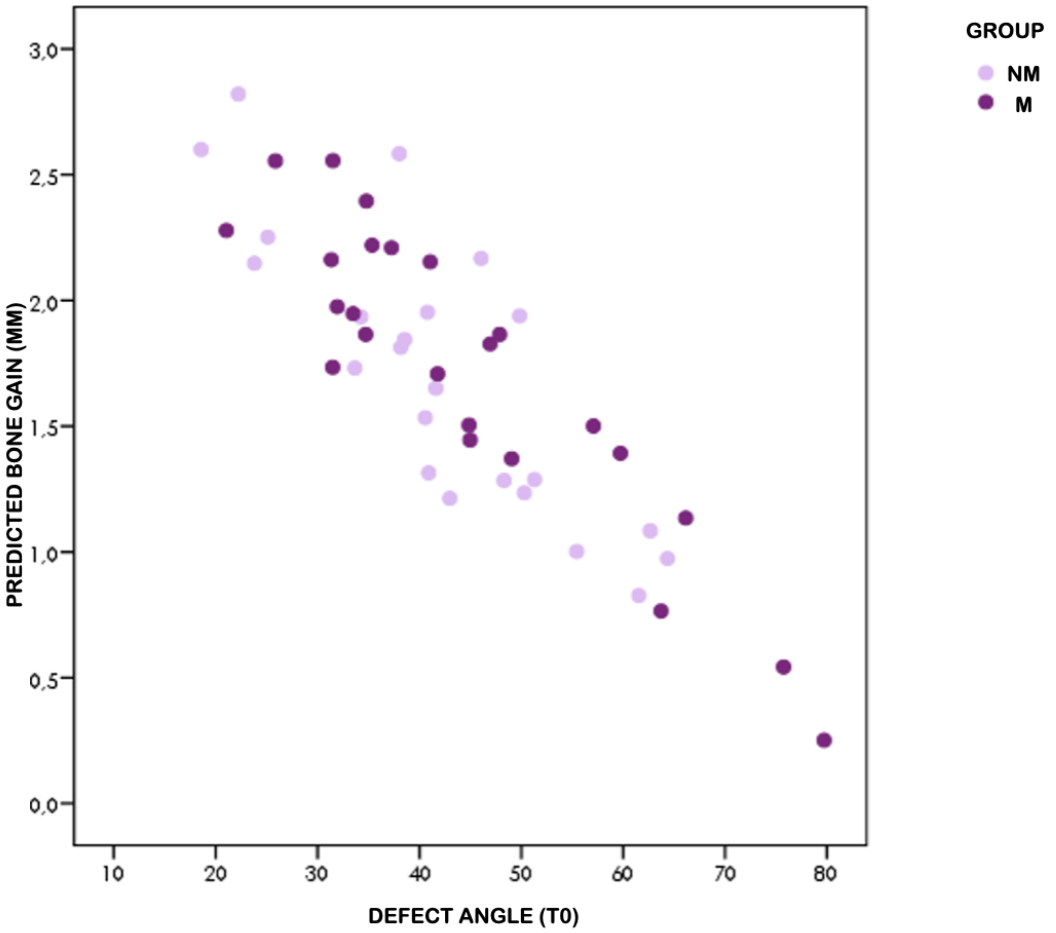
Figure 5. Influence of DA at T_0 on MBL gain at T_2, stratified by study groups











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References

1. Schwarz F, Derks J, Monje A, Wang HL. Peri-implantitis. *J Periodontol* 2018;89 Suppl 1:S267-S290.

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. Monje A, Nart J. Management and sequelae of dental implant removal. *Periodontol 2000* 2022;88:182-200.

5. Figuero E, Graziani F, Sanz I, Herrera D, Sanz M. Management of peri-implant mucositis and peri-implantitis. *Periodontol 2000* 2014;66:255-273.

6. Gargallo-Albiol J, Tavelli L, Barootchi S, Monje A, Wang HL. Clinical sequelae and patients' perception of dental implant removal: A cross-sectional study. *J Periodontol* 2021;92:823-832.

7. Listl S, Fruhauf N, Dannewitz B, et al. Cost-effectiveness of non-surgical peri-implantitis treatments. *J Clin Periodontol* 2015;42:470-477.

8. 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.

9. 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.

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

19. 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.

20. 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.

21. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Int J Surg* 2011;9:672-677.

22. 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.

23. Monje A, Pons R, Insua A, Nart J, Wang HL, Schwarz F. Morphology and severity of peri-implantitis bone defects. *Clin Implant Dent Relat Res* 2019;21:635-643.

24. 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.

25. Berglundh T, Armitage G, Araujo MG, et al. Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Periodontol* 2018;89 Suppl 1:S313-S318.

26. Mombelli A, van Oosten MA, Schurch E, Jr., Land NP. The microbiota associated with successful or failing osseointegrated titanium implants. *Oral Microbiol Immunol* 1987;2:145-151.

27. Monje A, Vera M, Munoz-Sanz A, Wang HL, Nart J. Suppuration as diagnostic criterium of peri-implantitis. *J Periodontol* 2020.

28. Serino G, Sato H, Holmes P, Turri A. Intra-surgical vs. radiographic bone level assessments in measuring peri-implant bone loss. *Clin Oral Implants Res* 2017;28:1396-1400.

29. Khoshkam V, Chan HL, Lin GH, et al. Reconstructive procedures for treating peri-implantitis: a systematic review. *J Dent Res* 2013;92:131S-138S.

30. Monje A, Mesquita PF. Clinical considerations in the surgical management of peri-implantitis lesions in the esthetic zone. *J Esthet Restor Dent* 2022.

31. 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.

32. 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.

33. 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.

34. 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.

35. 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.

36. 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.

37. Mott DA, Mailhot J, Cuenin MF, Sharawy M, Borke J. Enhancement of osteoblast proliferation in vitro by selective enrichment of demineralized freeze-dried bone allograft with specific growth factors. *J Oral Implantol* 2002;28:57-66.

38. Lagervall M, Jansson LE. Treatment outcome in patients with peri-implantitis in a periodontal clinic: a retrospective study. *J Periodontol* 2013;84:1365-1373.

39. Kopp SL, Ramseier CA, Ratka-Kruger P, Woelber JP. Motivational Interviewing As an Adjunct to Periodontal Therapy-A Systematic Review. *Front Psychol* 2017;8:279.

40. Alcouffe F. "Spontaneous" oral hygiene: a predictor for future preventive behavior? *Community Dent Oral Epidemiol* 1989;17:120-122.

41. Sanz M, Schwarz F, Herrera D, et al. Importance of keratinized mucosa around dental implants: Consensus report of group 1 of the DGI/SEPA/Osteology Workshop. *Clin Oral Implants Res* 2022;33 Suppl 23:47-55.

42. Monje A, Blasi G. Significance of keratinized mucosa/gingiva on peri-implant and adjacent periodontal conditions in erratic maintenance compliers. *J Periodontol* 2019;90:445-453.

43. Perussolo J, Souza AB, Matarazzo F, Oliveira RP, Araujo MG. Influence of the keratinized mucosa on the stability of peri-implant tissues and brushing discomfort: A 4-year follow-up study. *Clin Oral Implants Res* 2018;29:1177-1185.

44. Roccuzzo M, Grasso G, Dalmasso P. Keratinized mucosa around implants in partially edentulous posterior mandible: 10-year results of a prospective comparative study. *Clin Oral Implants Res* 2016;27:491-496.

45. Ravida A, Saleh I, Siqueira R, et al. Influence of keratinized mucosa on the surgical therapeutical outcomes of peri-implantitis. *J Clin Periodontol* 2020;47:529-539.

46. Zigdon H, Machtei EE. The dimensions of keratinized mucosa around implants affect clinical and immunological parameters. *Clin Oral Implants Res* 2008;19:387-392.

47. Perussolo J, Matarazzo F, Dias DR, Oliveira RP, Araujo MG. The effect of brushing discomfort on peri-implant health in sites exhibiting inadequate keratinized mucosa width: A cross-sectional study. *Clin Oral Implants Res* 2022.

48. 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.

49. Alcouffe F. Oral hygiene behavior: differences between men and women. *Clin Prev Dent* 1989;11:6-10.

50. Cha J, Wadhwani C, Wang M, Hokett SD, Katancik J. Instrument Selection and Application Used to Probe Dental Implants. *Int J Oral Maxillofac Implants* 2019;34:115-123.

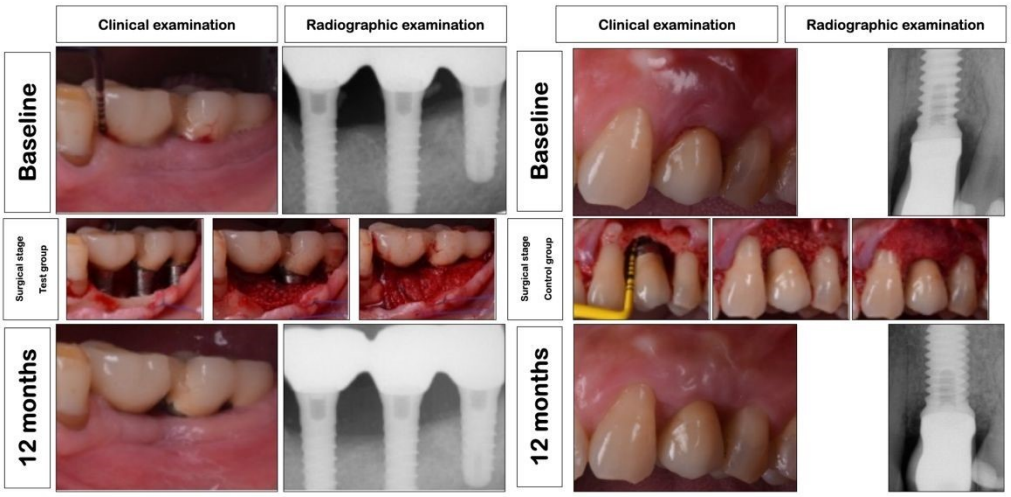

Table 1. Description of peri-implant clinical/radiographic parameters at baseline (T_0), 6 months (T_6) and 12 months (T_{12}). Intra-group estimations obtained from a generalized linear

model with repeated measures by generalized estimation equations (GEE). *P* values are expressed with Bonferroni's correction.

		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***
PPD max (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
REC (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	
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***

SD: standard deviation; PPD: probing pocket depth; max: maximum; msBI: modified sulcular bleeding index; SUP: suppuration; KM: keratinized mucosa; mPI: modified plaque index; REC: mucosal recession; MBL: marginal bone level; WD: width of the intra-bony defect; DA: angle of the intra-bony defect

*p<0.05; **p<0.01; ***p<0.001