Minimal invasiveness in the reconstructive treatment of peri-implantitis defects

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

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ABSTRACT

Peri-implantitis is a plaque-associated pathological condition occurring in tissues around dental implants, clinically characterized by increased peri-implant probing pocket depth and progressive loss of supporting bone. Consequently, to arrest further disease progression and to increase the chance to obtain re-osseointegration, surgical reconstructive procedures have been adopted. In particular, following a paradigm gathered from periodontal therapy, recent protocols have underlined the importance of a minimally invasive approach to optimize the outcomes of therapy while minimizing the risks of post-operative complications. The present review summarizes the level of evidence on the surgical reconstructive protocols focusing on the new approaches aimed to minimized surgical trauma and post-operative patient's discomfort underlining pros and cons of each treatment modality.

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1. Introduction

Peri-implantitis was defined in the 2018 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions as a biofilm-mediated pathological condition occurring in the tissues surrounding dental implants, characterized by peri-implant mucosal inflammation and progressive bone loss (1). Different treatments have been proposed for peri-implantitis, including non-surgical and surgical approaches, with mechanical and/or chemical surface decontamination, use of antimicrobial products and various surgical techniques (i.e. access flaps, resective or reconstructive procedures) (2). While non-surgical treatment seems to provide modest and non-predictable outcomes (3), different surgical approaches have proven to be more effective in terms of disease resolution (4, 5).

In the treatment of peri-implantitis, the classical surgical approach entails a mucoperiosteal flap, the removal of the granulation tissue and the detoxification of the contaminated implant surface. However, while non-reconstructive surgical approaches (i.e access flaps or resective surgery) aim to arrest further progression of the disease, reconstructive procedures aim to regenerate the intrabony component of the osseous defect. Nowadays, the decision-making process in the selection of the surgical technique in the treatment of peri-implantitis is based on the configuration of the peri-implant bone defect. As most peri-implantitis lesions feature a combined defect configuration including a supracrestal (class II) as well as an intra-bony component (classes Ia-e) (6), a surgical procedure combining implantoplasty at the supracrestal and buccally exposed implant surfaces (i.e. class Ib and Ic defects), concomitant to the application of bone substitute materials (or other regenerative approaches) at the intrabony defect component has been proposed, yielding positive results (7).

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A recent systematic review with meta-analyses, on the efficacy of the reconstructive surgical treatment in peri-implantitis-related bone defects showed that these techniques may lead to a larger improvements in marginal bone levels and defect fill over open-flap debridement (OFD) (8). However, no statistically significant differences could be observed for clinical parameters, such as probing depth (PD) or bleeding on probing (BOP). Nevertheless, subset meta-analyses could not be conducted to analyze confounders of the outcomes. Hence, it could be hypothesized that, similarly to what occurs in regenerative procedures around teeth, diagnostic/pre-operative considerations, flap design, the choice of biomaterials/adjuncts, suturing techniques, etc. may influence the short- and long-term outcomes, including the patient perception of the treatment, the incidence of complications and the morbidity/invasiveness of the intervention (9-13) in the reconstructive therapy of peri-implantitis lesions.

It is, therefore, the aim of the present review to describe the factors and techniques that may contribute to minimal invasiveness in the reconstructive treatment of peri-implantitis defects. To fulfill this objective, a systematic search, to comprehensively evaluate the available scientific literature, on minimally invasive reconstructive approaches in the surgical treatment of peri-implantitis lesions, has been performed.

2. Electronic search

A systematic search strategy was conducted to evaluate the existing body of evidence on minimal invasive strategies used in reconstructive therapy for the management of peri-implantitis.

Eligibility criteria

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The eligibility criteria were as follows: 1) clinical studies on reconstructive therapy of peri-implantitis, including "combined" approaches (i.e. resective/implantoplasty plus reconstructive); 2) randomized clinical trials (RCTs), controlled clinical trials (CCTs), or prospective/retrospective case series, with a minimum of 10 patients (5 per group in controlled studies).

Screening strategy

The electronic search was performed in Medline via PubMed. The search was limited to human subjects and to studies reported in English. The search strategy was an update of the one prepared for the European Workshop of Periodontology on Bone Regeneration (8), adding the term "minimal invasiveness" [i.e. (((((((((peri implantitis) OR peri-implantitis) OR periimplantitis)) AND ((((((surgical treatment) OR surgery) OR surgical) OR reconstructive) OR regenerative) OR regeneration))) NOT (((review) NOT in vitro) NOT animal))) AND ((minimal*) OR invasive*)].

Results of the systematic screening

The initial electronic search identified 808 records in PubMed. However, after screening for titles and abstracts, only two recently published manuscripts focusing on reconstructive therapy of peri-implantitis were identified (14, 15). Therefore, it was decided to remove the term "minimal invasiveness" from the search strategy and update the search from February 2018 to July 2021. This search yielded 305 articles published since February 2018. After abstract screening and full-text evaluation, 19 manuscripts corresponding to 18 investigations fulfilled the inclusion criteria. The hand search identified 6 additional manuscripts. However, it must be noted that most of these manuscripts did not describe any particular technique that could be considered "minimally invasive" neither evaluate patient reported outcome measures (PROMs). Therefore, it was decided that, for the present review, only those manuscripts resulting from the described search and the ones identified for the XV European Workshop on Periodontology (8) were considered. Thus,

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studies included were those which presented reconstructive approaches, that may be considered minimally invasive, or that proposed innovative techniques, devices or adjuncts that may end up into less morbidity for the patient, independently if that was properly evaluated or not. Further considerations related with the diagnostic examinations, the incidence of complications and the factors influencing the long-term results were also considered for the inclusion in the review.

3. Minimal invasiveness in reconstructive therapy of peri-implantitis: Myths and realities

By definition, "minimal invasiveness" refers to diagnostic or therapeutic techniques that limit the invasiveness while increasing treatment predictability alongside with accuracy. A minimal invasive therapy should therefore lead to an uneven and smooth healing process that resulting into a reduced/minimal sequalae when compared to conventional approaches. In the arena of periodontal regeneration, this term has been used for over than three decades to describe procedures that pursued less invasion by means of minimal flap elevation (16) (17) (18). These strategies frequently include "papilla preservation" techniques and have claimed the use of micro-surgical instruments and magnification to enhance access and visibility. These modalities have certainly led to effective outcomes in terms of clinical attachment level and radiographic bone gains while reducing marginal recession and papilla collapse (10). Therefore, their implementation in the management of peri-implantitis lesions might be suitable to reduce soft tissue changes that are frequently exhibited after disease resolution (19). Nonetheless, it is important to note a few drawbacks that may limit "minimal invasion" in the therapy of peri-implantitis: 1) comprehensive mechanical and/or chemical and/or pharmacological and/or electrolytic implant surface detoxification is key in succeeding and therefore, access is demanded (20), 2) peri-implantitis bone lesions are ~2x larger in size than periodontal lesions (21); 3) peri-implantitis is often associated with local potentially predisposing factors such as the lack of keratinized mucosa (22) or inadequate implant position, and peri-implantitis bone lesions rarely present a pure

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circumferential infra-osseous defect configuration (23) (24). Hence, the clinician must be aware that any attempt to pursue minimal invasiveness may conflict with long-term disease resolution.

As stated in the XV European Workshop on Periodontology, the evidence on the efficacy of reconstructive therapy at peri-implantitis related defects is limited, due to the large variability of the results, even if it seems that a greater improvement in marginal bone level and in radiographic defect fill is expected (8). Results from the present systematic review did not yield enhanced methods that might be considered of minimal invasiveness. Moreover, the search did not identify studies that addressed PROMs. In order to provide a more detailed view of the different aspects that may lead to minimal invasive procedures, the studies have been grouped according to: 1) surgical (e.g. new flap designs, suturing techniques, etc.) and prosthodontic factors (e.g. prostheses modifications), 2) the use of products or devices that may impact upon invasiveness and morbidity (e.g. growth factors, lasers, electrolytic cleaning, etc.), 3) the use of antimicrobial adjuncts to grafting materials (e.g. vancomycin, doxycycline, etc.).

1. *Surgical and prosthodontic factors (Table 1)*

Only one manuscript presents a "minimally invasive" surgical technique and fulfills the inclusion criteria of the present electronic search (25). This pilot study included 10 patients with 10 implants diagnosed of peri-implantitis and presenting a contained peri-implant defect, as determined clinically and radiographically. The proposed *Mini-Invasive Surgical Approach* (MISA) consists on the elevation of a flap to access the peri-implantitis defect only from one side (commonly the palatal/lingual), leaving the other side intact and limiting as much as possible the mesio-distal extension of the flap, avoiding vertical incisions and preserving the interdental papillae. According to the authors, healing was uneventful, and no relevant pain, hematoma or edema were noted. However, even if

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mean PD was reduced after 1-year, treatment success, expressed as a composite outcome, was not presented and the mean maximum PD at the studied implants was 7.9 mm at the end of the follow-up.

Although they do not fulfill the pre-established inclusion criteria related with the sample size (10 patients), it is worth to present some case reports describing innovative techniques (26-30).

The *Circumferential Occlusal Access Procedure* (COAP) aims to solve some of the difficulties that may appear during regenerative procedures, such as a shallow vestibule, a thin mucosa or sites without keratinized tissue (26). These features may increase the risk for membrane exposure, in case a barrier membrane use, with the consequent contamination and eventual loss of the graft (31). In this technique, both the decontamination of the implant surface and the bone grafting, if indicated, are performed through the peri-implant sulcus. First, a collar of soft tissue surrounding the implant is removed using a curette/scalpel circularly around the implant, down to the base of the bone, to remove the inflamed tissue. In a second phase, if bone grafting is indicated, an interproximal knife is used to lift the inner part of the soft tissue surrounding the implant to create a pouch, the bone substitute is placed in the defect, and a collagen membrane, with a punch hole in the center, is placed over the head of the implant and into the pouch, covering the bone grafting material without the need of any suture. As, in contrast to periodontal lesions, peri-implantitis lesions may frequently present bacterial invasion within the connective tissue (32), the proposed approach, that includes peri-implant mucosa curettage and also favors clot stability, may somehow improve the results of non-surgical therapy, that has proven to be ineffective in most of the studies (33). A conceptually very similar technique was proposed in 2021 (29), with the name of *Peri-implant Excisional Procedure and Access Surgery* (PEAS). This technique proposes the removal of the granulation tissue through a peri-implant circular incision, together with a chemical (hydrogen peroxide) and mechanical decontamination (with a titanium brush). However, two prerequisites

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are needed: i) presence of enough keratinized tissue to avoid leaving the implant site without keratinized mucosa; and ii) possibility to remove the prostheses.

Other minimally invasive surgical approaches have been proposed, including the use of a videoscope to remove foreign bodies (e.g. cement, titanium particles, etc.) (27), and the so-called *Sub-Periosteal Peri-Implant Augmented Layer* (SPAL) technique, in which a periosteal pouch is created after performing a partial-thickness flap to stabilize a xenograft (28). This technique had been previously presented for the horizontal augmentation of the ridge at the time of implant placement in case of presence of dehiscence-type defects (34). The rationale for the technique relies upon the stabilization of the graft particles and the clot by the periosteal layer, that may also act as a source of osteogenic cells (35). However, further clinical and pre-clinical research is needed in order to determine the beneficial effects of this approach. The SPAL technique is described with detail in the section 6 of the present work (Figure 1).

Apical accesses have been proposed in periodontal regenerative procedures to avoid placing incisions directly on top of the bone defects, following the *Non-Incised Papilla Surgical Approach* (NIPSA) (36, 37). Similarly, a modified surgical approach using the Er:YAG laser has been proposed to overcome the soft tissue recession that may appear after peri-implantitis defects regeneration (*Laser-Assisted Peri-implant Defect Regeneration*, LAPIDER) (30). In this technique, a horizontal mucosal incision, 4-5 mm apically from the marginal mucosa, is made to gain access to the implant apex, and, after mucoperiosteal coronal flap elevation, the implant surface is debrided with the Er:YAG laser, followed by grafting with particulate autogenous bone and a connective tissue graft. Conceptually, this approach avoids cutting the interdental papilla complex and the mucosal margin recession that may occur if incisions are made on top of the bone defect (Figure 2). However, long term results are missing and definitive evidence in favor of this technique should be derived from properly conducted RCTs.

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Finally, as inappropriate prosthetic designs may hamper adequate oral hygiene practices and have proven to be associated with peri-implantitis prevalence (38), it is likely that prosthetic modifications allowing the access to oral hygiene could be helpful in order to obtain the best results for peri-implantitis therapy. Even if it was performed in patients with peri-implant mucositis, a recently published RCT clearly demonstrated that modifying the prostheses to allow a better access for biofilm control resulted into a higher percentage of disease resolution at 6 months (66%) than in those cases in which just mechanical instrumentation was performed (9.6%) (39).

2. Use of products or devices that may impact on invasiveness and morbidity (Table 2)

Historically, the decision-making process for reconstructive procedures of peri-implantitis defects has been influenced by the classical periodontal and dental implant surgery. Specifically, the principles of guided tissue regeneration using a barrier membrane on top of the surgically treated area with the aim to stabilize the graft and exclude the epithelium ingrowth have been widely used (40). One of the first proposals was published by Khoury and co-workers in 2001 treating 41 deep peri-implant defects with either autogenous bone grafts alone or in combination with resorbable or non-resorbable membranes using a submerged healing approach. The reported clinical and radiographic data showed comparable results with no additional benefits for the sites that received a barrier membrane (31). One aspect of the proposed technique that has to be underlined is that the bone block harvesting procedure require a second surgical site with consequently increased patient's morbidity. Furthermore, the application of an e-PTFE membrane may increase the risk of membrane exposure. Therefore, it is clear from these author's perspective that such an intervention cannot be considered minimally invasive and should be avoided to minimize patient's discomfort and limit the risk of post-operative complications. Similar conclusions were drawn by Roos-Jansäker and co-workers in a 5-year RCT where the adjunct benefit of a resorbable membrane

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use (test group) was investigated compared to a regenerative procedure without membrane (control group): the obtained results displayed a significant improvement in term of clinical and radiographic outcomes without detecting statistically significant difference between the two groups (41). Consequently, despite the lack of a solid evidence, the routinely use of a barrier membrane as a pivotal step in the surgical reconstructive treatment of peri-implantitis might not be recommended. Nevertheless, in cases of deep non-contained defects in order to stabilize the grafting material, its application might be taken into consideration.

Another controversial aspect is which should be considered as the ideal grafting material. Historically, intra-orally harvested autogenous bone has been proposed due to its excellent characteristics (42). Nevertheless, increased patient's morbidity, limited quantity of available material and high pattern of resorption have been described as major disadvantages (43). Consequently, clinicians have searched for alternative materials with good clinical results the aim to reconstruct the lost peri-implant hard tissue and ideally promote re-osseointegration (44).

Growth factors, such as enamel matrix derivatives (EMD) or platelet-rich fibrin (PRF), have been proposed to improve the outcomes of reconstructive procedures around peri-implantitis defects. Scaffolds with PRF contain several bioactive molecules, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF-β) and insulin-like growth factor (IGF), that may be progressively released during matrix fibrin remodeling in early healing stages. This ability has shown to be able to improve the outcomes of access flaps in the surgical treatment of peri-implantitis, in terms of PD reduction and gains in clinical attachment level (CAL) (45). Particularly interesting is a prospective study evaluating the clinical effect of PRF combined with guided bone regeneration (GBR) in the reconstruction of peri-implantitis defects in 80 patients (46). Patients were randomly allocated to the control group, treated with a bone substitute following GBR principles, or to test group, who received a mixture of PRF and a bone substitute covered with PRF membranes. Interestingly, levels of pain, 24 hours after the surgery, were significantly lower in the test group, indicating that the

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addition of PRF may influence post-operative PROMs. Better results were also provided in terms of PD reduction and regenerated bone density. However, another investigation performed in Turkey, using demineralized bovine bone mineral (DBBM), together with a different fibrin clot membrane [the so-called concentrated growth factors (CGF) obtained by separation from centrifuged venous blood, using a different centrifuge machine and presenting different mechanical characteristics in terms of stiffness], failed to provide any further improvement in the regenerative treatment of peri-implantitis defects when compared to DBBM plus a native collagen membrane (47). No evaluation of patient´s perspective of treatment was carried out in this study. If the morbidity associated with venous blood collection is overcome by the theoretically better post-operative perception by the patient, needs to be properly evaluated in future clinical trials evaluating PROMs more thoroughly.

Finally, amelogenins (EMD) could also accelerate wound healing by osteopromotive and antibacterial effects (48). Specifically, EMD have proven to be able to promote blood vessels formation and expression of TGF-β, vascular endothelial growth factor (vEGF) and fibronectin (49). The first report of the possible use of EMD for the treatment of peri-implantitis was a case series of 51 patients with a 3.0-7.5 years follow-up (50). Encouraging results after application of EMD to the decontaminated implant surface, followed by defect-filling with either a xenograft or an allograft previously hydrated with a PDGF and covered with a collagen membrane or a connective tissue graft, were observed. PD reductions were ≈5 mm, while radiographic bone level gains were ≈3 mm. Similar results were presented in another case series of 30 patients with peri-implantitis, performed in Australia (51), in which after surgical access and debridement, defects were filled with a mixture of DBBM, EMD and doxycycline powder. After a 3-year period, results were considered successful for 56.6% of the implants (PD<5 mm, no further bone loss >10%, no BOP/suppuration, no recession >0.5 mm in anterior implants or >1.5 mm for posterior implants).

Also testing EMD, a RCT on the regenerative treatment of peri-implantitis, with or without adjunctive EMD, including 29 patients was conducted in Sweden, providing results after 5 years of follow-up (52, 53). The primary outcome variable was implant survival, that

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was significantly superior in the EMD group than in the non-EMD group after 3 years (100% vs 83%), but no after 5 years (85% vs 75%) (53). However, the multivariate modelling identified the use of EMD, together with bone level changes, as positively associated with implant survival, while suppuration, smoking habit or presence of residual pockets after treatment, as negatively associated. It seems clear that larger studies are needed before reaching any conclusion regarding the potential beneficial effects of EMD in the treatment of peri-implantitis and if the use of this biologic contributes to reduce the invasiveness of these procedures.

If re-osseointegration is considered a requirement for successful reconstructive treatment of peri-implantitis, it is compulsory to effectively eliminate the biofilm from the implant surface, as well as achieved a proper decontamination. Several mechanical and/or chemical methods for implant surface decontamination have been used in clinical studies focused on the reconstructive therapy of peri-implantitis defects, showing radiographic bone fill. However, re-osseointegration rates in animal studies range 39-46% (54). Therefore, even if it is doubtful that re-osseointegration is mandatory to achieve stable peri-implant tissues, ideally it should be the aim of regenerative procedures.

Electrolytic cleaning is one of the approaches that have been proposed to decontaminate the implant surface with the objective of favoring re-osseointegration (55). The mode of action of this approach consists on the application of an electrolyte solution (i.e. sodium formiate) pumped by a device through a platinized ring acting as an anode and sprayed on the implant surface. The electrolysis produces hydrogen cations (H^+) that penetrate and break up the biofilm (56). The clinical outcomes of electrolytic cleaning versus electrolytic cleaning plus a powder-spray system using erythritol was investigated by Schlee and coworkers in a RCT (57, 58). In brief, 24 patients (34 implants) with peri-implantitis were surgically treated with these decontamination devices, followed by an augmentation procedure using autogenous bone mixed with DBBM, in a 50:50 ratio, covered with a native collagen membrane and using a submerged healing approach. Six out of 34 implants had to be extracted due to re-infection throughout the 18-month follow-up.

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Significant radiographic bone fill and PD reduction were observed in the remaining implants in both groups, without significant differences among them.

Another device that has been proposed as an effective tool for implant surface decontamination is ER:YAG laser (59, 60). Specifically, a recent pilot RCT evaluated the adjunctive benefit of Er:YAG laser in the regenerative surgical therapy of peri-implantitis, using a mixture of human allograft with DBBM and covered with an acellular dermal matrix membrane (61). In this 6-month study, using the laser led to a significantly higher PD reduction, but other parameters were not significantly affected [i.e. CAL gain and marginal bone level]. Lasers may be useful, not just in the decontamination of the implant surface due to their bactericidal capacity, but also to attenuate the inflammation of the peri-implant tissues (62), although as it occurs with non-surgical periodontal therapy, the increased costs may hamper its effectiveness (63).

3. Use of antimicrobial adjuncts to grafting materials (Table 3)

Despite mechanical instrumentation, it is difficult to completely remove biofilms from implant surfaces. Therefore, local and/or systemically delivered antimicrobials have been evaluated, to understand if their adjunctive use may improve the results of both the non-surgical and surgical treatment of peri-implantitis (5, 64-68). Specifically, local antimicrobials may provide added value, since they may solve some of the problems related with the prescription of systemic antimicrobials, such as the development of antibiotic resistances or the limited penetration into bone tissue (69, 70), and they may be useful in the chemical decontamination of the exposed implant surfaces. However, none of these reports evaluated the impact of the antimicrobial adjuncts on the invasiveness of these interventions, and therefore, RCTs are needed to confirm if the notable results observed in some cases when arresting peri-implant inflammation also correlate with a lower invasiveness.

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Recently, a RCT evaluating the effect of systemic metronidazole as an adjunct to non-surgical treatment of peri-implantitis has been published (68). Even if this approach may not be considered a reconstructive procedure, the results showed significant radiographic bone fill as a consequence of the treatment provided. While previous reports on non-surgical therapy of peri-implantitis tended to show more modest results (33), the mean radiographic bone gain attained in the test group of this study (consisting on a mechanical non-surgical debridement session, including mucosal curettage, and prescription of metronidazole 500 mg, three times a day, for seven days accounted for 2.3 mm after 12 months, exceeding by far the one observed in other studies, where an average of ≈0.5 mm was observed after non-surgical therapy used with adjunctive metronidazole plus amoxicillin (71, 72). Indeed, the radiographic bone gain in the study of Blanco et al. is comparable to the 1.9 mm reported after surgical reconstructive treatment (8) (Figure 3). This could be explained by the baseline severity of the peri-implantitis lesions, the type of implants treated and the stability of clot formation after non-surgical debridement. Sadly, PROMs were not reported, although it seems plausible thinking that the invasiveness of this non-surgical treatment should be lower than that of classic reconstructive procedures following a GBR approach. Therefore, leaving aside relevant considerations on the use of adjunctive systemic antibiotics, such as the increase in antibiotic resistance, the adjunctive use of systemic metronidazole as an adjunct to non-surgical treatment of advanced peri-implantitis lesions resulted into promising results after 12 months, although larger studies with longer follow-up and a more comprehensive evaluation of patient´s perspective are needed.

4. How could the need and number of invasive pre-operative diagnostic examinations be minimized?

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It is expected that the incidence of peri-implant biological complications will tend to increase in the near future as the number of dental implants placed increase year by year (73) (74). In this sense, it is important to emphasize that one of the tasks for clinicians is to develop a long-term effective supportive periodontal/peri-implant therapy (SPT) program in order to intercept peri-implantitis at an early stage, when reconstructive treatment could still be feasible with a higher percentage of expected success. In particular, since the morphology of the peri-implantitis defects may potentially influence the reconstructive outcomes, it seems reasonable to assume that assessing the configuration of the bone lesions once they are developed may optimize the surgical approach and, therefore, reduce the invasiveness.

As stated by the 2017 World Workshop on Classification of Periodontal and Peri-implant Diseases and Conditions, recording peri-implant PD on a regular basis has a clear prognostic value without any drawback, as it has been demonstrated that gentle probing produces no harm to the supra-crestal connective tissue (75). On the other hand, even though radiographic imaging is an essential component of treatment planning, exposure to ionizing radiation must always be justified and result in a net benefit to the patient (76) (Figure 4).

According to Jacobs et al. (76) the use of cone beam computed tomography (CBCT) after the insertion of dental implants should be limited to specific postoperative complications that required implant retrieval (e.g. neurovascular trauma), and should not be indicated for regular follow-up to obtain a three-dimensional view of the peri-implant tissues. During SPT, clinicians are encouraged to use peri-implant bi-dimensional bone level measures "on correctly taken periapical radiographs, even if has had no true prognostic value and considering that only the proverbial tip of the iceberg of the actual size and morphology of a defect seen". If radiographic images

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should be requested even with no signs of augmented peri-implant probing and the frequency of radiographic examinations are still a matter of controversy.

CBCT is frequently considered an useful tool for peri-implantitis diagnosis and treatment planning, though the underestimation of defect severity may affect the prognosis and clinical decision-making (77). Clinicians need to be cautious in establishing prognoses and treatment based on CBCT assessment, as it has been reported to offer modest performance in the characterization of peri-implantitis defects, due to poor resolution and/or the presence of artifacts. Indeed, beam-hardening is the phenomenon that occurs when an x-ray beam passes through an object, resulting in selective attenuation of lower energy photons. In CBCT, beam hardening from a very dense target, namely the implant and the prosthetic reconstruction, may result in characteristic artifacts which render the precise determination of bone difficult. However, even if CBCTs were found to be less accurate when interpreting the severity of bone loss, they were perfectly accurate identifying peri-implant bone morphology, potentially justifying the request for a 3-D examination before a surgical approach to a peri-implantitis defect (Figure 5). In a recent 5-year prospective study, Roccuzzo et al. (78) found that the reconstructive treatment of single peri-implantitis intrabony defects resulted in a high implant survival rate in patients who fully adhered to SPT visits, but the resolution of the lesions did not seem to be significantly associated with the defect configuration.

Taking all these factors into account, and in order to minimize the invasiveness of diagnostic examinations, a tailored SPT program should be adapted to patient's need and risk profile, and include routine peri-implant probing, but not necessarily radiographic images (79). In case of augmented PDs, with the concomitant presence of bleeding and/or suppuration, a conventional periapical radiograph can be performed to establish a more accurate diagnosis of defect morphology and to plan the most indicated surgical approach (23) (Figure 6).

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5. Complications, sequelae and morbidity in the reconstructive treatment of peri-implantitis.

The use of a bone graft with or without the combination of barrier membranes or other regenerative technologies (e.g. EMD), is the most common approach in the reconstructive treatment of peri-implant defects. Autologous bone is the gold standard for regenerative purposes due to its properties, however it has certain limitations such as the limited availability and the increased intra-surgical morbidity associated to the donor site. The use of a xenograft may overcome both limitations and reduce surgical time, thus reducing intra-operative morbidity. Several studies have compared the use of autologous grafts versus xenografts, reporting statistically significant better results in radiographic bone fill, mean PD reduction and mean suppuration reduction with the use of a xenograft (80). However, its impact on patient´s morbidity or surgical time has not been adequately studied. The combination of PRF with a xenograft has been reported to significantly reduce patient´s pain 24 hours after surgery, when compared with flap curettage and granulation tissue removal alone, as well as to obtain higher reductions in plaque index, sulcus bleeding index and PD, 7 days post-surgery, and greater defect fill 60 days after surgery (46). These results suggest that PRF combined with a bone graft may have a positive effect in terms of short-term recovery and healing, when compared with access flap alone. However, further studies with longer follow-up periods are needed to confirm the superiority of this approach.

The reconstructive treatment of peri-implant defects is not exempt of intra- and post-surgical complications. The most frequent complications reported in the literature are soft tissue dehiscences, membrane exposures, infection and sequester formation (47, 81). The placement of barrier membranes increases the risk for post-surgical complications, especially non-resorbable (31) and acellular dermal matrix membranes (61). To date, we have not identified in the literature any minimally invasive surgical approach for the

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reconstructive therapy of peri-implantitis that had demonstrated the capability to reduce the occurrence of such complications, when compared with conventional approaches.

6. Patient-reported outcome measures (PROMs) and clinical sequelae in the reconstructive treatment of peri-implantitis.

The reconstructive treatment of peri-implant defects has proven to induce favorable results in terms of radiographic bone levels and defect fill (8). However, changes in mucosal margin are scarcely reported (8, 81). Mucosal recession after peri-implantitis surgery seems to be of greater magnitude when resective (82) or combined (resective plus reconstructive) surgical approaches are performed, when compared with reconstructive approaches (83). In fact, there are reports of mucosal margin level gain after peri-implant reconstructive procedures (83-86). However, these results do not seem to be predictable, and they are also not consistent among studies. A recent systematic review with meta-analysis on the efficacy of the reconstructive treatment of peri-implantitis estimated a statistically significant weighted mean (WM) recession of -0.65 mm (95% confidence interval; CI: [-0.97; -0.33]), 12 months after treatment (8), while a previous systematic review had reported a non-statistically significant WM mucosal gain of 0.22 mm (95% CI: [-0.07; 0.51]) after 36 months of follow-up. Nevertheless, and independently of the surgical approach chosen for the treatment of peri-implantitis, the occurrence of mucosal recession after surgery should be avoided to the best of our capabilities, since the unveiling of the grayish metallic cervical portion of the implant to the oral cavity, independently of its size, may compromise patients' aesthetics and satisfaction, especially when it occurs on implants located in the anterior region (15).

The use of minimally invasive flaps could minimize the apical migration of the peri-implant mucosal margin after surgery. Fletcher and Tarnow proposed in 2018 a flapless approach called the *Circumferential Occlusal Access Procedure* (COAP) as an alternative to

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conventional flaps (26), that has already been explained in section 3a. This surgical approach aims to reduce the risk of mucosal recession and membrane exposure due to soft tissue dehiscences by accessing the implant through a circumferential pouch surrounding the implant.

The *Sub-Periosteal Peri-Implant Augmented Layer* (SPAL) technique has been proposed recently by Trombelli and coworkers (28), for the regenerative treatment of peri-implant defects. This technique consists of raising a partial thickness flap in the buccal aspect of the implant, leaving the periosteal layer on top of the implant and the surrounding peri-implant bone crest. After this, a full thickness pouch is created by tunneling the periosteal layer to expose the peri-implant defect. Careful debridement of the granulation tissue and implant surface decontamination is performed before filling the intrabony component of the defect with a bone xenograft. To stabilize the graft, the periosteal layer is sutured to the palatal flap. In those cases where there is a lack of adequate keratinized mucosa or the graft cannot be covered completely with the periosteal layer, a connective tissue graft is added on top of the periosteal flap. Last, the mucosal layer is coronally advanced and sutured covering the whole area. This technique has been presented in a proof-of-principle case report of three subjects and 4 implants with peri-implant defects class Ib/Ic and a follow up of 6 months, reporting favorable results in both radiographic and clinical variables, including an improvement in the mucosal margin levels for all implants, with reductions in mucosal recession, when compared with baseline, and increments in the band of keratinized tissue. Even if the technique deserves further evaluation in long-term clinical trials to evaluate its invasiveness, it seems that it may be reduced, as the split-thickness flap allows for a smaller access when compared to traditional flaps used for GBR (i.e. including releasing incisions). What is more, it seems to provide favorable results without using a membrane, which may impact surgical time, costs and incidence of complications.

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The surgical approach with the name *Laser-Assisted Peri-Implant Defect Regeneration* (LAPIDER) has proposed a novel technique aiming at reconstructing both hard and soft tissues around dental implants (30). It consists in a horizontal mucosal incision, 5 mm apical to the marginal mucosa, combined with a supraperiosteal preparation in apical direction and a subperiosteal full-thickness flap in coronal direction, that allows access to the implant surface. The peri-implant defect is debrided and detoxified with Er:YAG laser. Afterwards, the bone defect is filled with an autogenous graft from the mandibular ramus, and a connective tissue graft is placed underneath the subperiosteal layer to increase mucosal thickness. A bilayer suturing technique is performed in the periosteum and the mucosa. A case report, with a follow up of 12 months, is presented in the paper, with favorable results in both clinical and radiographic variables, and a noticeable improvement in keratinized mucosa thickness, width, and marginal level.

Nevertheless, these techniques should be further evaluated in properly designed clinical trials, with a sufficient sample size and follow-up period, to adequately evaluate their effectiveness.

Regarding patient satisfaction with the treatment provided, there is a noteworthy absence of data on PROMs in the literature regarding the regenerative treatment of peri-implantitis lesion (8). One RCT (87), comparing the use of a nanocrystalline hydroxyapatite versus the use of a natural bone mineral graft in combination with a collagen membrane for the reconstructive treatment of peri-implantitis lesions, reported a high degree of satisfaction among participants, related to the fact that the treatment provided allowed them to maintain their implants for a longer period of time. Another multi-centre RCT (88), comparing the use of a xenograft and a resorbable collagen membrane versus open flap debridement of peri-implantitis lesions, also reported high and comparable levels of satisfaction with the treatment provided in both groups, after 6 weeks and 12 months of follow-up. Furthermore, no differences in pain medication intake or pain scores were found among subjects from test and control groups. Even though the use of minimally invasive surgical

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approaches has been claimed to reduce patient morbidity and improve post-operative healing, these aspects are frequently overlooked and not registered or nor reported in the literature. Therefore, strong conclusions cannot be made with regards to PROMs in the minimally invasive reconstructive therapy of peri-implantitis.

7. Factors influencing the invasiveness and outcomes of the reconstructive therapy of peri-implant defects.

The outcomes of reconstructive therapy have been proved to be influenced by multiple factors, including the surgical approach, the implant characteristics, site-specific features and the bone defect configuration. The management of peri-implantitis is based upon the empiric knowledge derived from the therapy of periodontitis-related defects. It is understood that supra-crestal defect configurations lack of reparative potential and, therefore, the therapy may result unsuccessful independently of the reconstructive strategy. On the other hand, infra-osseous defect configurations are prone to exhibit favorable outcomes whenever reconstructive measures are applied (23). In fact, Schwarz et al. (2010) explored the impact of infra-osseous defect configuration upon the reconstructive outcomes of peri-implantitis lesions using deproteinized bovine bone mineral in combination with a collagen membrane. Interestingly, it was demonstrated that circumferential-like defects (class Ie) yielded more favorable outcomes when compared to dehiscence or crater-like defects (89). Later on, Aghazadeh et al. (2020) tested the association of defect configuration and depth upon the clinical and radiographic outcomes of reconstructive therapy using either autogenous bone or deproteinized bovine bone mineral combined with a resorbable barrier membrane. It was shown that defect fill was significantly correlated to initial defect depth and that bone fill was significantly enhanced in circumferential-like defects when compared to 2- or 3-wall defects (90). Therefore, well-contained defects are potential candidates to minimal invasiveness by means of a less invasive surgical approach (simplifying access and the number of incisions) or the application of reconstructive therapy not necessary fulfilling the principle of guided bone

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regeneration in terms of using a barrier membrane. On the other side, Roccuzzo et al. (2021) in a long-term cohort study using deproteinized bovine bone mineral with 10% collagen did not find an association between defect configuration and implant survival (91). This could be explained due to the stable nature of the bone filler, in contrast of traditional bone substitutes that are presented in particles and may be less prone to reach stability within the defect. Thus, based upon existing evidence, it seems that defect configuration may affect at a certain extent the invasiveness and the reconstructive outcomes of peri-implantitis (Figure 7-8).

Other site-specific feature speculated to influence the reconstructive outcome in the management of peri-implantitis are soft tissue characteristics. It seems reasonable that, given that implants lacking keratinized and attached mucosa are more exposed to peri-implantitis, soft tissues may play a role on disease resolution (22, 92, 93). Nonetheless, evidence up to date is conflicting. Ravidà et al. (2020) in a retrospective study showed that the presence of keratinized mucosa had a negligible influence neither on the clinical resolution nor on bone levels at peri-implantitis implants after surgical therapy (94). It must be disclosed that this study was conducted in a university setting and that also non-reconstructive strategies to manage peri-implantitis were included, what may have influenced the results. However, other trials have shown favorable outcomes in the surgical non-reconstructive management of peri-implantitis when the soft tissues were simultaneously conditioned by means of free epithelialized mucosal grafts in scenarios associated with lack of keratinized mucosa (95, 96). Therefore, inconclusive statements can be drawn based upon existing evidence; nevertheless, it seems reasonable that those cases where the lack of keratinized mucosa played a role on the onset and progression may further lead to recurrence if the soft tissues are not conditioned simultaneously or staged to the anti-infective therapy (Figure 9).

Debate has been further evoked by the suitability of the approach in terms of submerging the reconstructive compartment to promote an aseptic healing. Schwarz et al. (2006) in a preclinical experimental-induced peri-implantitis model showed that submerged healing

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improved the surgical treatment outcome, in particular, concerning the radiographic and the histomorphometric findings (97). In line with this, Roos-Jansaker et al. (2011) in a 3-year prospective clinical study tested the influence of submerging the implant for 6 months after reconstructive therapy (98). It was demonstrated that less optimal outcomes were shown when a transmucosal versus a submerged healing approach was applied. More recently, Monje et al. (2020) in a prospective 1-year case series reported favorable outcomes in terms of disease resolution and radiographic bone gain in 85% of the cases that initially exhibited 3-wall defect configurations and that underwent submerged healing for 8-10 weeks (99). In contrast, Astolfi et al. (2021) in a retrospective case series observed no benefit of a submerged healing approach for 8-10 weeks when compared to transmucosal healing (15). Hence, although evidence seems to favor submerged healing protocols, this must not be recommended in the daily basis for all cases given that 1) removing the prosthesis may alter patient satisfaction, 2) the achievement of a tension-free primary closure may lead to a distortion of the mucosal margin that may lead to a loss of the buccal band of keratinized mucosa, and 3) in combined defects it might be challenging to achieve primary closure and also to lead to residual pockets. It is the authors' opinion that, whenever possible, the prosthetic supra-structure must be temporally removed to attain better access for an efficient surface detoxification prior to grafting. Moreover, prosthesis that somehow predisposed the onset of the disease by an inadequate emergence design, must be modified or replaced to promote adequate access for self-performed oral hygiene measures (39). It is worth noting that the association of peri-implantitis and the inadequate design of prosthetic supra-structures has been reported to be high (23, 38, 100).

Another element that has demonstrated to be relevant in the reconstructive outcomes of peri-implantitis relates to the implant surface topographic characteristics. Wetzel et al. (1999) in a preclinical study aimed at analyzing the influence of the implant surface [titanium plasma spray (TPS) versus sand blasted, large grit, acid-etched (SLA) versus smooth surface] on reconstructive and non-reconstructive procedures to manage experimental peri-implantitis in dogs. Interestingly, it was found that implant surface

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characteristics did not significantly influence bone gain along a 6-month follow-up study period (101). Shibli et al. (2006) compared four different surface characteristics (commercially pure titanium surface, TPS, acid-etched, surface-oxide sandblasted) in reconstructive therapy carried out after experimental peri-implantitis in dogs. It was demonstrated in a 5-month follow-up histologic examination that bone gain and re-osseointegration was independent to surface characteristics but relied upon surface detoxification by means of photosensitization therapy using a diode laser (102). Almohandes et al. (2019) aimed at investigating the influence of surface characteristics (TiO-blasting/acid-etched versus smooth/acid-etched) on the reconstructive outcomes of experimental peri-implantitis in dogs using a variety of bone grafting substitutes with or without a barrier membrane (103). It was shown that smooth-surface implants outperformed in terms of radiographic bone gain, level of re-osseointegration and resolution of disease when compared to moderately rough-surface implants. Rodriguez et al. (2018) compared the resolution of experimental peri-implantitis in dogs of two different implant surface characteristics [resorbable blast texture (RBT) versus laser microtextured] by means of reconstructive therapy using bovine bone and a barrier membrane (104). It was found that laser microtextured implants led to a difference of 0.4 mm in bone gain when compared to RTM-surface implants. This is aligned with the clinical findings from Roccuzzo et al. (2017-2020), that in a clinical study evaluating reconstructive therapy of peri-implantitis defects using deproteinized bovine bone mineral with 10% collagen observed that both implant survival and disease resolution were influenced by implant surface characteristics. In particular, disease resolution was found in 42% of the SLA implants and in 29% of the TPS implants. Furthermore, SLA outperformed TPS in terms of implant survival by 25% (105) (106). Therefore, existing evidence points out the significance of implant surface characteristics on the expected outcomes in the reconstructive treatment of peri-implant defects.

8. Long term outcomes of the reconstructive therapy of peri-implant defects.

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Despite the large body of evidence recently published, very few studies have reported long-term outcomes of the reconstructive therapy of peri-implantitis defects. More specifically, Roos-Jansaker et al. (2011) showed in a 3-year case control study a mean bone fill of 1.3 mm or 1.6 mm if treatment consisted on bone grafting alone or on bone grafting combined with a barrier membrane, respectively (98). Authors noted that a key to maintain the long-term outcomes was the adherence to a strict supportive peri-implant maintenance program. In fact, the plaque index decreased from 40% to 10% during the first year and remained stable during the following 2 years (98). Froum et al. (2012) in a 3- to 7.5-year follow-up case series using a combination of enamel matrix derivative and platelet-derived growth factor mixed with mineralized allografts or deproteinized bovine bone mineral and a barrier membrane or a connective tissue graft, bone level gain ranged from 3 mm to 3.75 mm with no implant loss along the study period. Authors stated that all the patients were adhered to a strict supportive peri-implant maintenance program (50). Schwarz et al. (2013) in a 4-year RCT showed a mean 1.4 mm of clinical attachment level gain using two different surface detoxification strategies and grafted using deproteinized bovine bone mineral and a collagen membrane. Authors demonstrated that the method of surface detoxification (i.e. ER:YAG laser or plastic curettes plus cotton pellets plus sterile saline) did not influence in the resolution of peri-implantitis (85).

La Monaca et al. (2018) evaluated in a 5-year case series study the maintenance of reconstructive outcomes achieved by means of mineralized allograft and a resorbable membrane. It was demonstrated that at 1-year follow-up disease resolution was 91%. Nonetheless, at 5-year assessment, only bleeding on probing reduction was statistically significant compared to baseline and no difference was found in probing pocket depth and in peri-implant bone level when compared to baseline records. Thus, it could be hypothesized that there is a progressive decrease in bone filling after the reconstructive treatment of peri-implant defects (107). More recently, Roccuzzo et al. (2020) in the, up to date, clinical study with the longest follow-up demonstrated that the reconstructive outcomes after using deproteinized bovine bone mineral with 10% collagen can be maintained in a 10-year basis if periodic supportive peri-implant maintenance is provided. Implant survival was 80% and 55% for SLA and TPS implants, respectively. In light of the

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findings, authors concluded that the decision making in managing peri-implantitis should be further based upon implant surface topographic features (106). Irrespective of the intervention applied, the available evidence stresses out the need of adhering into a strict SPT to sustain long-term outcomes (108). In fact, minimally invasive strategies for SPT are valid and effective aiming at reducing pain/discomfort while enhancing the effectiveness of SPT. For instance, the use of glycine powder air polishing devices during SPT have demonstrated higher efficiency in removing biofilm and achieving higher patient satisfaction at implant-supported prosthesis when compared to traditional methods. This finding may indicate the time is reduced and the comfort achieved during SPT is higher using this strategy as prosthesis might be unnecessary to be removed during SPT to reach a plaque-free environment (109).

9. Summary and conclusions

The primary goal of the treatment of peri-implantitis is to arrest the progression of peri-implant bone loss. Particularly, reconstructive therapies are more ambitious, seeking the reconstruction of the hard and/or soft tissues lost as a result of the disease. The concepts of minimal invasiveness evaluated in the reconstructive treatment of peri-implantitis lesions include specific flap designs (26, 28, 30) with the aim to minimize the surgical trauma, preserving the interproximal tissue and the position of the peri-implant mucosal margin, in an analogous manner to the different "papilla preservation" and apical accesses techniques that have demonstrated to minimize the surgical trauma in regenerative periodontal treatment (11, 36). However, most of these techniques have been presented as case reports and no controlled clinical trials (CCTs or RCTs) have been performed to show the superiority of these techniques over conventional surgical accesses. In any case, it has to be acknowledged that as long as implant position, defect configuration and/or soft tissue characteristics may impact the flap design, it is difficult to conduct RCTs including comparable lesions.

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Classically, the reconstructive treatment of peri-implant defects has followed the principles of guided bone regeneration, that is, the use of barrier membranes that prevent the migration of epithelial cells in the defect. However, although there may be controversy from the biological point of view that the isolated use of bone substitutes can favor re-osseointegration, the truth is that different clinical trials have not been able to determine the clinical advantages of the use of barrier membranes (41). What is more, probably the use of barrier membranes requires more experience and impacts also upon the morbidity of these procedures, as long as surgical sites need to be wider for the adequate placement of the membrane. Other products that may potentially influence invasiveness and morbidity are the use of several bioactive molecules or growth factors (e.g. EMD, PRF) (49) that may promote neovascular events. Nevertheless, the effect of growth factors or other devices that may be helpful in implant decontamination has not been studied properly and no recommendations for its use could be done now.

Similarly, antimicrobial adjuncts may be useful in the treatment of peri-implantitis, although it remains questionable if its use should be exclusively restricted to machined implants (65). Interestingly, recent studies report positive results after the use of systemic metronidazole concomitant to the non-surgical therapy of peri-implantitis (68), with increased radiographic bone gain in the longest follow-up, suggesting that, in opposition to previous knowledge, non-surgical treatment may be a minimally invasive method to solve a relevant percentage of peri-implantitis cases (≈50%) and that time is an important factor to consider before moving into surgery.

Surprisingly, no information could be retrieved from the studies considered in this review regarding PROMs or aesthetic parameters, which may be relevant as long as the surgical treatment of peri-implantitis may result into Buccal Soft Tissue Dehiscences (BSTD). Therefore, it is unclear if minimally invasive reconstructive procedures may diminish the incidence of BSTD.

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In conclusion, the invasiveness of the reconstructive procedures for peri-implantitis lesions has not been properly evaluated, so it is difficult for these authors to provide guidelines in the topic. Anyway, it seems reasonable to think that minimizing the trauma on the peri-implant soft tissues may provide some benefits from the patient´s perspective, although this has to be always balanced with a proper access for implant surface decontamination.

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References

1. Berglundh T, Armitage G, Araujo MG, Avila-Ortiz G, Blanco J, Camargo PM, 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-S8.

2. Figuero E, Graziani F, Sanz I, Herrera D, Sanz M. Management of peri-implant mucositis and peri-implantitis. Periodontol 2000. 2014;66(1):255-73.

3. Suarez-Lopez Del Amo F, Yu SH, Wang HL. Non-Surgical Therapy for Peri-Implant Diseases: a Systematic Review. J Oral Maxillofac Res. 2016;7(3):e13.

4. Berglundh T, Wennstrom JL, Lindhe J. Long-term outcome of surgical treatment of peri-implantitis. A 2-11-year retrospective study. Clin Oral Implants Res. 2018;29(4):404-10.

5. Gonzalez Regueiro I, Martinez Rodriguez N, Barona Dorado C, Sanz-Sanchez I, Montero E, Ata-Ali J, et al. Surgical approach combining implantoplasty and reconstructive therapy with locally delivered antibiotic in the treatment of peri-implantitis: A prospective clinical case series. Clin Implant Dent Relat Res. 2021;23(6):864-73.

6. Schwarz F, Herten M, Sager M, Bieling K, Sculean A, Becker J. Comparison of naturally occurring and ligature-induced peri-implantitis bone defects in humans and dogs. Clin Oral Implants Res. 2007;18(2):161-70.

7. 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(3):337-42.

8. Tomasi C, Regidor E, Ortiz-Vigon A, Derks J. Efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects. A systematic review and meta-analysis. J Clin Periodontol. 2019;46 Suppl 21:340-56.

9. 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(8):643-7.

10. Cortellini P, Pini-Prato G, Nieri M, Tonetti MS. Minimally invasive surgical technique and enamel matrix derivative in intrabony defects: 2. Factors associated with healing outcomes. Int J Periodontics Restorative Dent. 2009;29(3):257-65.

11. Cortellini P, Tonetti MS. Clinical and radiographic outcomes of the modified minimally invasive surgical technique with and without regenerative materials: a randomized-controlled trial in intra-bony defects. J Clin Periodontol. 2011;38(4):365-73.

12. Sanz M, Tonetti MS, Zabalegui I, Sicilia A, Blanco J, Rebelo H, et al. Treatment of intrabony defects with enamel matrix proteins or barrier membranes: results from a multicenter practice-based clinical trial. J Periodontol. 2004;75(5):726-33.

.

13. Jepsen S, Heinz B, Jepsen K, Arjomand M, Hoffmann T, Richter S, et al. A randomized clinical trial comparing enamel matrix derivative and membrane treatment of buccal Class II furcation involvement in mandibular molars. Part I: Study design and results for primary outcomes. J Periodontol. 2004;75(8):1150-60.

14. 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(11):1047-60.

15. Astolfi V, Gomez-Menchero A, Rios-Santos JV, Bullon P, Galeote F, Rios-Carrasco B, 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).

16. Takei HH, Han TJ, Carranza FA, Jr., Kenney EB, Lekovic V. Flap technique for periodontal bone implants. Papilla preservation technique. J Periodontol. 1985;56(4):204-10.

17. Cortellini P, Prato GP, Tonetti MS. The modified papilla preservation technique. A new surgical approach for interproximal regenerative procedures. J Periodontol. 1995;66(4):261-6.

18. Cortellini P, Prato GP, Tonetti MS. The simplified papilla preservation flap. A novel surgical approach for the management of soft tissues in regenerative procedures. Int J Periodontics Restorative Dent. 1999;19(6):589-99.

19. Sanz-Martin I, Cha JK, Sanz-Sanchez I, Figuero E, Herrera D, Sanz M. Changes in peri-implant soft tissue levels following surgical treatment of peri-implantitis: A systematic review and meta-analysis. Clin Oral Implants Res. 2021;32 Suppl 21:230-44.

20. Renvert S, Polyzois I, Maguire R. Re-osseointegration on previously contaminated surfaces: a systematic review. Clin Oral Implants Res. 2009;20 Suppl 4:216-27.

21. Carcuac O, Berglundh T. Composition of human peri-implantitis and periodontitis lesions. J Dent Res. 2014;93(11):1083-8.

22. Monje A, Blasi G. Significance of keratinized mucosa/gingiva on peri-implant and adjacent periodontal conditions in erratic maintenance compliers. J Periodontol. 2019;90(5):445-53.

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(4):635-43.

24. Wehner C, Bertl K, Durstberger G, Arnhart C, Rausch-Fan X, Stavropoulos A. Characteristics and frequency distribution of bone defect configurations in peri-implantitis lesions-A series of 193 cases. Clin Implant Dent Relat Res. 2021;23(2):178-88.

25. Iorio-Siciliano V, Gasparro R, Blasi A, Mortellaro C, Sammartino G, Wang HL, et al. Treatment of a peri-implantitis defect using a mini-invasive surgical approach (MISA) and deproteinized bovine bone mineral with 10% collagen: a case series. J Biol Regul Homeost Agents. 2019;33(6 Suppl. 2):41-7 DENTAL SUPPLEMENT.

26. Fletcher P, Tarnow DP. Circumferential Occlusal Access Procedure (COAP): Novel Minimally Invasive Surgical Approach for Treatment of Peri-Implantitis- A Case Series. Compend Contin Educ Dent. 2018;39(9):626-35.

.

27. Wilson TG, Jr. A New Minimally Invasive Approach for Treating Peri-Implantitis. Clin Adv Periodontics. 2019;9(2):59-63.

28. Trombelli L, Severi M, Farina R, Simonelli A. Sub-Periosteal Peri-Implant Augmented Layer Technique to Treat Peri-Implantitis Lesions. Clin Adv Periodontics. 2020;10(4):169-74.

29. Lee J, Choi JU, Lee JB, Dds IR, Lee YM. A Case Report of a 2-Year Follow-up of Minimally Invasive Surgery in Peri-implantitis: Peri-implant Excisional Procedure and Access Surgery (PEAS). J Oral Implantol. 2021.

30. Noelken R, Al-Nawas B. A modified surgical approach for hard and soft tissue reconstruction of severe periimplantitis defects: laser-assisted periimplant defect regeneration (LAPIDER). Int J Implant Dent. 2020;6(1):22.

31. Khoury F, Buchmann R. Surgical therapy of peri-implant disease: a 3-year follow-up study of cases treated with 3 different techniques of bone regeneration. J Periodontol. 2001;72(11):1498-508.

32. Berglundh T, Gislason O, Lekholm U, Sennerby L, Lindhe J. Histopathological observations of human periimplantitis lesions. J Clin Periodontol. 2004;31(5):341-7.

33. Renvert S, Roos-Jansaker AM, Claffey N. Non-surgical treatment of peri-implant mucositis and peri-implantitis: a literature review. J Clin Periodontol. 2008;35(8 Suppl):305-15.

34. Trombelli L, Severi M, Pramstraller M, Farina R. A simplified soft tissue management for peri-implant bone augmentation. Int J Oral Maxillofac Implants. 2019;34(1):197-204.

35. Nobuto T, Suwa F, Kono T, Taguchi Y, Takahashi T, Kanemura N, et al. Microvascular response in the periosteum following mucoperiosteal flap surgery in dogs: angiogenesis and bone resorption and formation. J Periodontol. 2005;76(8):1346-53.

36. Moreno Rodriguez JA, Caffesse RG. Nonincised Papillae Surgical Approach (NIPSA) in Periodontal Regeneration: Preliminary Results of a Case Series. Int J Periodontics Restorative Dent. 2018;38(Suppl):s105-s11.

37. Moreno Rodriguez JA, Ortiz Ruiz AJ, Zamora GP, Pecci-Lloret M, Caffesse RG. Connective Tissue Grafts with Nonincised Papillae Surgical Approach for Periodontal Reconstruction in Noncontained Defects. Int J Periodontics Restorative Dent. 2019;39(6):781-7.

38. Serino G, Strom C. Peri-implantitis in partially edentulous patients: association with inadequate plaque control. Clin Oral Implants Res. 2009;20(2):169-74.

39. 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(10):1050-60.

40. Needleman I, Tucker R, Giedrys-Leeper E, Worthington H. Guided tissue regeneration for periodontal intrabony defects--a Cochrane Systematic Review. Periodontol 2000. 2005;37:106-23.

41. 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(11):1108-14.

42. Myeroff C, Archdeacon M. Autogenous bone graft: donor sites and techniques. J Bone Joint Surg Am. 2011;93(23):2227-36.

.

43. Kamal M, Gremse F, Rosenhain S, Bartella AK, Holzle F, Kessler P, et al. Comparison of Bone Grafts From Various Donor Sites in Human Bone Specimens. J Craniofac Surg. 2018;29(6):1661-5.

44. Madi M, Htet M, Zakaria O, Alagl A, Kasugai S. Re-osseointegration of Dental Implants After Periimplantitis Treatments: A Systematic Review. Implant Dent. 2018;27(1):101-10.

45. Hamzacebi B, Oduncuoglu B, Alaaddinoglu EE. Treatment of Peri-implant Bone Defects with Platelet-Rich Fibrin. Int J Periodontics Restorative Dent. 2015;35(3):415-22.

46. Sun G, Cao L, Li H. Effects of platelet-rich fibrin combined with guided bone regeneration in the reconstruction of peri-implantitis bone defect. Am J Transl Res. 2021;13(7):8397-402.

47. Isler SC, Soysal F, Ceyhanlı T, Bakırarar 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(5):703-12.

48. Miron RJ, Sculean A, Cochran DL, Froum S, Zucchelli G, Nemcovsky C, et al. Twenty years of enamel matrix derivative: the past, the present and the future. J Clin Periodontol. 2016;43(8):668-83.

49. Maymon-Gil T, Weinberg E, Nemcovsky C, Weinreb M. Enamel Matrix Derivative Promotes Healing of a Surgical Wound in the Rat Oral Mucosa. J Periodontol. 2016;87(5):601-9.

50. Froum SJ, Froum SH, Rosen PS. Successful management of peri-implantitis with a regenerative approach: a consecutive series of 51 treated implants with 3- to 7.5-year follow-up. Int J Periodontics Restorative Dent. 2012;32(1):11-20.

51. 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(6):583-91.

52. Isehed C, Holmlund A, Renvert S, Svenson B, Johansson I, Lundberg P. Effectiveness of enamel matrix derivative on the clinical and microbiological outcomes following surgical regenerative treatment of peri-implantitis. A randomized controlled trial. J Clin Periodontol. 2016;43(10):863-73.

53. 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(6):744-53.

54. Tastepe CS, van Waas R, Liu Y, Wismeijer D. Air powder abrasive treatment as an implant surface cleaning method: a literature review. Int J Oral Maxillofac Implants. 2012;27(6):1461-73.

55. Schlee M, Naili L, Rathe F, Brodbeck U, Zipprich H. Is Complete Re-Osseointegration of an Infected Dental Implant Possible? Histologic Results of a Dog Study: A Short Communication. J Clin Med. 2020;9(1).

56. Ratka C, Weigl P, Henrich D, Koch F, Schlee M, Zipprich H. The Effect of In Vitro Electrolytic Cleaning on Biofilm-Contaminated Implant Surfaces. J Clin Med. 2019;8(9).

.

57. Schlee M, Rathe F, Brodbeck U, Ratka C, Weigl P, Zipprich H. Treatment of Peri-implantitis-Electrolytic Cleaning Versus Mechanical and Electrolytic Cleaning-A Randomized Controlled Clinical Trial-Six-Month Results. J Clin Med. 2019;8(11).

58. 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).

59. Takasaki AA, Aoki A, Mizutani K, Kikuchi S, Oda S, Ishikawa I. Er:YAG laser therapy for peri-implant infection: a histological study. Lasers Med Sci. 2007;22(3):143-57.

60. Aoki A, Mizutani K, Schwarz F, Sculean A, Yukna RA, Takasaki AA, et al. Periodontal and peri-implant wound healing following laser therapy. Periodontol 2000. 2015;68(1):217-69.

61. 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(3):378-88.

62. Hauser-Gerspach I, Stubinger S, Meyer J. Bactericidal effects of different laser systems on bacteria adhered to dental implant surfaces: an in vitro study comparing zirconia with titanium. Clin Oral Implants Res. 2010;21(3):277-83.

63. Sanz M, Herrera D, Kebschull M, Chapple I, Jepsen S, Beglundh T, et al. Treatment of stage I-III periodontitis-The EFP S3 level clinical practice guideline. J Clin Periodontol. 2020;47 Suppl 22:4-60.

64. Heitz-Mayfield LJA, Salvi GE, Mombelli A, Faddy M, Lang NP. Anti-infective surgical therapy of peri-implantitis. A 12-month prospective clinical study. Clin Oral Implants Res. 2012;23(2):205-10.

65. Carcuac O, Derks J, Charalampakis G, Abrahamsson I, Wennstrom J, Berglundh T. Adjunctive Systemic and Local Antimicrobial Therapy in the Surgical Treatment of Peri-implantitis: A Randomized Controlled Clinical Trial. J Dent Res. 2016;95(1):50-7.

66. Nart J, de Tapia B, Pujol À, 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(6):2199-207.

67. Nart J, Pons R, Valles C, Esmatges A, Sanz-Martin I, Monje A. Non-surgical therapeutic outcomes of peri-implantitis: 12-month results. Clin Oral Investig. 2020;24(2):675-82.

68. Blanco C, Pico A, Dopico J, Gandara P, Blanco J, Linares A. Adjunctive benefits of systemic metronidazole on non-surgical treatment of peri-implantitis. A randomized placebo-controlled clinical trial. J Clin Periodontol. 2022;49(1):15-27.

69. Sukumar S, Martin FE, Hughes TE, Adler CJ. Think before you prescribe: how dentistry contributes to antibiotic resistance. Aust Dent J. 2020;65(1):21-9.

70. Fraimow HS. Systemic antimicrobial therapy in osteomyelitis. Semin Plast Surg. 2009;23(2):90-9.

71. Shibli JA, Ferrari DS, Siroma RS, Figueiredo LC, Faveri M, Feres M. Microbiological and clinical effects of adjunctive systemic metronidazole and amoxicillin in the non-surgical treatment of peri-implantitis: 1 year follow-up. Braz Oral Res. 2019;33(suppl 1):e080.

.

72. Stein JM, Hammacher C, Michael SS. Combination of ultrasonic decontamination, soft tissue curettage, and submucosal air polishing with povidone-iodine application for non-surgical therapy of peri-implantitis: 12 Month clinical outcomes. J Periodontol. 2017.

73. Gaviria L, Salcido JP, Guda T, Ong JL. Current trends in dental implants. J Korean Assoc Oral Maxillofac Surg. 2014;40(2):50-60.

74. De Ry SP, Roccuzzo A, Lang NP, Heitz-Mayfield LJ, Ramseier CA, Sculean A, et al. Evaluation of the implant disease risk assessment (IDRA) tool: A retrospective study in patients with treated periodontitis and implant-supported fixed dental prostheses (FDPs). Clin Oral Implants Res. 2021;32(11):1299-307.

75. Etter TH, Hakanson I, Lang NP, Trejo PM, Caffesse RG. Healing after standardized clinical probing of the perimplant soft tissue seal: a histomorphometric study in dogs. Clin Oral Implants Res. 2002;13(6):571-80.

76. Jacobs R, Salmon B, Codari M, Hassan B, Bornstein MM. Cone beam computed tomography in implant dentistry: recommendations for clinical use. BMC Oral Health. 2018;18(1):88.

77. Insua A, Ganan Y, Macias Y, Garcia JA, Rakic M, Monje A. Diagnostic Accuracy of Cone Beam Computed Tomography in Identifying Peri-implantitis-Like Bone Defects Ex Vivo. Int J Periodontics Restorative Dent. 2021;41(6):e223-e31.

78. 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.

79. Monje A, Aranda L, Diaz KT, Alarcon MA, Bagramian RA, Wang HL, et al. Impact of Maintenance Therapy for the Prevention of Peri-implant Diseases: A Systematic Review and Meta-analysis. J Dent Res. 2016;95(4):372-9.

80. Aghazadeh A, Rutger Persson G, Renvert S. A single-centre randomized controlled clinical trial on the adjunct treatment of intra-bony defects with autogenous bone or a xenograft: results after 12 months. J Clin Periodontol. 2012;39(7):666-73.

81. Khoshkam V, Suárez-López Del Amo F, Monje A, Lin GH, Chan HL, Wang HL. Long-term Radiographic and Clinical Outcomes of Regenerative Approach for Treating Peri-implantitis: A Systematic Review and Meta-analysis. Int J Oral Maxillofac Implants. 2016;31(6):1303-10.

82. Romeo E, Ghisolfi M, Murgolo N, Chiapasco M, Lops D, Vogel G. Therapy of peri-implantitis with resective surgery. A 3-year clinical trial on rough screw-shaped oral implants. Part I: clinical outcome. Clin Oral Implants Res. 2005;16(1):9-18.

83. Deppe H, Horch HH, Neff A. Conventional versus CO2 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(1):79-86.

84. 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(6):857-63.

85. Schwarz F, Hegewald A, John G, Sahm N, Becker J. Four-year follow-up of combined surgical therapy of advanced peri-implantitis evaluating two methods of surface decontamination. J Clin Periodontol. 2013;40(10):962-7.

.

86. Solakoglu Ö, Filippi A. Regenerative Therapy of Peri-Implantitis: Clinical and Radiologic Documentation of 16 Consecutive Patients With a Mean Follow-Up of 3 Years. J Oral Implantol. 2019;45(2):145-53.

87. 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(9):807-14.

88. Renvert S, Roos-Jansåker 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(10):1266-74.

89. 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(5):449-55.

90. 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(1):33.

91. 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(10):1209-17.

92. 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(12):1177-85.

93. 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(4):491-6.

94. Ravida A, Saleh I, Siqueira R, Garaicoa-Pazmino C, Saleh MHA, Monje A, et al. Influence of keratinized mucosa on the surgical therapeutical outcomes of peri-implantitis. J Clin Periodontol. 2020;47(4):529-39.

95. Monje A, Blasi G, Nart J, Urban IA, Nevins M, Wang HL. Soft Tissue Conditioning for the Surgical Therapy of Peri-implantitis: A Prospective 12-Month Study. Int J Periodontics Restorative Dent. 2020;40(6):899-906.

96. Solonko M, Regidor E, Ortiz-Vigon A, Montero E, Vilchez B, Sanz M. Efficacy of keratinized mucosal augmentation with a collagen matrix concomitant to the surgical treatment of peri-implantitis: A dual-center randomized clinical trial. Clin Oral Implants Res. 2021.

97. 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(8):584-95.

98. 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(6):590-7.

99. 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(3):342-50.

.

100. Pons R, Nart J, Valles C, Salvi GE, Monje A. Self-administered proximal implant-supported hygiene measures and the association to peri-implant conditions. J Periodontol. 2021;92(3):389-99.

101. Wetzel AC, Vlassis J, Caffesse RG, Hammerle CH, Lang NP. Attempts to obtain re-osseointegration following experimental peri-implantitis in dogs. Clin Oral Implants Res. 1999;10(2):111-9.

102. Shibli JA, Martins MC, Ribeiro FS, Garcia VG, Nociti FH, Jr., Marcantonio E, Jr. Lethal photosensitization and guided bone regeneration in treatment of peri-implantitis: an experimental study in dogs. Clin Oral Implants Res. 2006;17(3):273-81.

103. Almohandes A, Carcuac O, Abrahamsson I, Lund H, Berglundh T. Re-osseointegration following reconstructive surgical therapy of experimental peri-implantitis. A pre-clinical in vivo study. Clin Oral Implants Res. 2019;30(5):447-56.

104. Rodriguez JC, Koticha T, Eubanks DL, Rudek I, Molz FJ, Chiavaccini L, et al. Influence of Microtextured Implant Surfaces on Peri-implantitis and Its Treatment: A Preclinical Trial. Int J Oral Maxillofac Implants. 2018;33(1):51-7.

105. Roccuzzo M, Pittoni D, Roccuzzo A, Charrier L, Dalmasso P. Surgical treatment of peri-implantitis intrabony lesions by means of deproteinized bovine bone mineral with 10% collagen: 7-year-results. Clin Oral Implants Res. 2017;28(12):1577-83.

106. Roccuzzo M, Fierravanti L, Pittoni D, Dalmasso P, Roccuzzo A. Implant survival after surgical treatment of peri-implantitis lesions by means of deproteinized bovine bone mineral with 10% collagen: 10-year results from a prospective study. Clin Oral Implants Res. 2020;31(8):768-76.

107. 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(10):1025-37.

108. Roccuzzo M, Layton DM, Roccuzzo A, Heitz-Mayfield LJ. Clinical outcomes of peri-implantitis treatment and supportive care: A systematic review. Clin Oral Implants Res. 2018;29 Suppl 16:331-50.

109. Menini M, Delucchi F, Bagnasco F, Pera F, Di Tullio N, Pesce P. Efficacy of air-polishing devices without removal of implant-supported full-arch prostheses. Int J Oral Implantol (Berl). 2021;14(4):401-16.

Table 1. Scientific manuscripts proposing minimally invasive surgical techniques in the reconstructive treatment of peri-implantitis considered for this review.

Study	Intervention	Number of Patients (Number of Implants)	Outcomes
Iorio-Siciliano et al. (2019)	Mini-Invasive Surgical Approach (MISA) consisting on the elevation of a flap only on one side (palatal aspect)	10 (10)	Significant probing depth reduction and radiographic bone gain were noted, with minimal mucosal recession and limiting patient morbidity

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Fletcher and Tarnow (2018)	Circumferential Occlusal Access Procedure (COAP) a flapless surgical technique designed to access the contaminated implant surface through the removal of a collar of soft tissue adjacent to the implant	3 (4)	Bone fill and absence of bleeding on probing were observed 8-24 months after therapy. Minimal post-operative pain and swelling were reported.
Wilson (2019)	Videoscope-assisted minimally invasive surgical approach	1 (1)	No pain was reported after the procedure. No further bone loss but apparent bone fill was observed after one year, together with absence of deep pockets.
Trombelli et al. (2020)	Sub-Periosteal Peri-Implant Augmented Layer Technique (SPAL). In this technique a split-thickness flap is elevated leaving a periosteal layer creating a pouch to stabilize the xenograft. In case of insufficient Keratinized mucosa, a connective tissue graft was placed on the buccal aspect	3 (3)	Treatment resulted into significant reconstruction of the peri-implant support in absence of deep pockets or inflammation
Noelken and Al-Nawas (2020)	Laser-Assisted Peri-implant Defect Regeneration (LAPIDER). Horizontal mucosal incision 5 mm apical to the marginal mucosa, subperiosteal coronal flap elevation, debridement of the implant surface with Er:YAG laser, grafting with particulated autogenous bone + connective tissue.	1 (1)	Marginal Bone Levels (MBLs) improved interproximally, buccally and orally at the 1-year examination. Probing depths and recession decreased significantly, while the facial mucosa thickness improved.
Lee et al. (2021)	Peri-implant Excisional Procedure and Access Surgery (PEAS). After the disconnection of the prostheses, the granulation tissue was removed through a peri-implant circular incision in a similar manner to the excisional new attachment procedure (ENAP)	1 (1)	The surgical intervention was effective in arresting peri-implantitis as no further bone loss but bone fill was observed over a 2-year period.
Cortellini et al. (2021)	Reconstructive approaches for the treatment of peri-implantitis lesions using papilla preservation flaps (PPF) and minimally invasive surgery (MIST; i.e. exposing just 1-2 mm of the defect-associated residual bone crest, avoiding "passing" the papilla and releasing incisions if possible)	21 (21)	Primary wound closure was obtained in 100% of the sites. Significant reduction in BOP and PD was observed. Significant radiographic bone fill was observed and maintained throughout the 5 years of follow-up (≈2.5 mm). No discomfort or problem with daily activities was reported by the patients. Post-operative pain was of low intensity (ranging 10-24 on a 0-100 visual analog scale)

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Table 2. Studies evaluating products or devices that may impact upon the invasiveness and morbidity of reconstructive procedures in the treatment peri-implantitis lesions: interventions, number of patients/implants, and summary of main outcomes.

Study	Intervention	N patients (implants)	Outcomes
Froum et al. (2012)	Regenerative approach including surface decontamination, EMD, a combination of PDGF with DBBM or MFDBA, and the coverage with a collagen membrane or a subepithelial connective tissue graft	38 (51)	No implant was lost during the follow-up (3 to 7.5 years). PD reduction ranged 3-10 mm. Radiographic bone gain was 3.8 mm in those implants presenting a visible interproximal defect at the baseline examination. Bone sounding was performed in those cases in which the greatest bone loss was on the facial or oral aspect of the implant, accounting for a 3.0 mm bone gain.
Hamzacebi et al. (2015)	Conventional access flap surgery adding the application of PRF	19 (38)	PRF group demonstrated higher mean PD reduction and more CAL gain after 6 months
Isehed et al. (2016, 2018)	EMD in access flap surgery (RCT)	29 (29)	At the 3-year follow-up visit, 100% of the implants survived in the EMD group, while in the control group survival was 83%. At the 5-year follow-up appointment, survival rates were 85% of the implants in the EMD group vs 75% in the control group.
Isler et al. (2018)	Regenerative approach using DBBM covered either with a CM or CGF (RCT)	52 (52)	Treatment resulted into significant reductions of BOP and PD reduction in both groups at 6 and 12 months without significant differences among groups. Mean defect fill was also not statistically significant different between groups.
Mercado et al. (2018)	Surgical access and debridement, defects filled with a combined mixture of DBBM, EMD and doxycycline powder.	30 (30)	56.6% of the implants were considered successfully treated according to a composite outcome (PD<5 mm, no further bone loss>10%, no BOP/suppuration, no recession>0.5 mm for anterior implants and >1.5 mm for posterior implants) after 36 months
Schlee et al. (2019, 2021)	Regenerative approach with DBBM plus autogenous covered with a CM after decontamination with EC or combination of an EC and a powder spray (RCT)	24 (24)	Mean PD and BOP were significantly reduced, while significant radiographic bone fill was observed 18 months after therapy. No significant differences between groups were observed.
Sun et al. (2021)	Effect of adjunctive PRF to GBR with DBBM and a CM (RCT)	80 (80)	Pain and bleeding were significantly lower 24 hours and 7 days after surgery in the PRF group. Compared with the control group, the PRF group revealed significantly higher regenerated bone density 60 and 120 days after surgery.
Wang et al. (2021)	Effect of adjunctive of Er:YAG laser in the surface decontamination prior to a reconstructive procedure with a mixture of DBBM plus allograft and covered with an acellular dermal matrix membrane (RCT)	24 (NR)	Laser irradiation led to a significantly higher PD reduction 6 months after surgery. No differences were observed for CAL gain or radiographic linear bone gain.

RCT, randomized clinical trial; NR, not reported. EMD, enamel matrix derivative; PDGF, platelet-derived growth factor; DBBM, demineralized bovine bone mineral; MFDBA, mineralized freeze-dried bone allograft; PRF, platelet-rich fibrin; CM, collagen membrane; CGF, concentrated growth factor; EC, decontamination with an electrolytic method; GBR, guided bone regeneration procedures. PD, probing depth; CAL, clinical attachment level; BOP, bleeding on probing.

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Table 3. Studies proposing the use of antimicrobial adjuncts to grafting materials in the reconstructive treatment of peri-implantitis: intervention, number of patients/implants and summary of main outcomes.

Study	Intervention	N patients (implants)	Outcomes
Nart et al. (2018)	After mechanical and chemical decontamination, a vancomycin and tobramycin impregnated allograft was placed in the defect and covered with a collagen membrane allowing a non-submerged healing	13 (17)	No implant was lost. Significant reductions in BOP and PD. Mean radiographical intrabony defect filling was 86.7% ± 18.2%
La Monaca et al. (2018)	After mechanical debridement, chemical decontamination using hydrogen peroxide (3%), chlorhexidine (0.2%) and a tetracycline hydrochloride solution was performed before defect filling with mineralized dehydrated bone allograft and a resorbable membrane	34 (34)	At 1-year, no implant showed peri-implant bone loss ≥1.0 mm and 91% of the implants presented absence of PD ≥5 mm and absence of BOP. However, this percentage was 59% at the 5-year examination and 23% of the implants presented bone loss ≥1.0 mm
Gonzalez Regueiro et al. (2021)	Combined approach with implantoplasty of the supraosseous component together with the reconstruction of the intrabony defect using a bone substitute hydrated with a piperacillin/tazobactam 100/12.5 mg solution.	43 (43)	After 12-months 86% of the implants presented disease resolution according to a composite outcome (absence of BOP/suppuration, further bone loss ≤0.5 mm)

BOP, bleeding on probing; PD, probing reduction.

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Figures

Figure 1. Advanced peri-implantitis lesion exceeding 50% of the implant length. (a) Clinical presentation. Note profuse bleeding and suppuration, (b) periapical x-ray displays advanced bone loss with angular defects in the inter-proximal aspects, (c) upon surgical access a 3-wall defect (class Ib) is noted. Implantoplasty was used as adjunct method to detoxify the implant surface. The SPAL technique is performed, where the periosteum is attached to the alveolar bone and outlining the lesion to promote enhanced stability of bone (d) mineralized and demineralized bone allograft. (f) Clinical disease resolution was demonstrated at 12-month follow-up and (g) radiographic bone gain was evident

Figure 2. Peri-implantitis case scenario (a) clinical examination unveiled suppuration and increased pocket depth from baseline (b) upon clinical access a 3-wall (class Ib) defect configuration is noted. Note papilla preservation approach. A combination of (c) mineralized and (d) demineralized allograft were used for grafting after comprehensive surface detoxification by means of Ni-Ti brush and H_2O_2 for 2 minutes. (e) Disease was resolved at 15-month follow-up with minimal soft tissue alterations. (f) Note bone gain to flatten bone architecture.

Figure 3. Peri-implantitis case treated by means of non-surgical treatment with systemic metronidazole (500 mg every 8 hours for 7 days) a) Baseline periapical radiograph (December 2015) b) Radiographic bone gain (June 2021).

Figure 4. Several clinical scenarios characterized by increased peri-implant probing depth, bleeding and/or suppuration on probing which require additional radiographic 2-D evaluation

Figure 5. Patient erroneously referred for the treatment of peri-implantitis on implant 21. Note the absence of marginal clinical signs of peri-implant infection (BoP & Pus) (a) despite the complete resorption of the buccal bone wall (b). This clinical scenario did not require any treatment

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Figure 6. illustrates the case of a patient presenting peri-implantitis (a). Even though the conventional radiographic image does not show the infrabony defect (b), which is mainly on the palatal side of the implant, as it became visible at the time of regenerative surgery (c), careful probing under anesthesia eliminated the absolute need for a 3D image. Three years after surgical treatment, peri-implant tissues are healthy with minimal probing depth and no bleeding. There is no indication for a further radiographic examination (d).

Figure 7. Circumferential-like defects are indicated to reconstructive therapy due to the stability that the residual bony walls may provide for the grafting material. Note (a-b) frontal and occlusal views of class I defect configuration and the periapical radiographic image (c).

Figure 8. Class Ib peri-implantitis-related bone defects are the most frequent defect configuration. They are often associated with implants placed too buccally. This feature impacts the reconstructive procedure as bone regeneration in the buccal aspect of these implants is often compromised. (a) frontal view, (b) occlusal view.

Figure 9. In scenarios exhibiting minimal keratinized mucosa and slight crater-like defects, it may be preferable to select a non-reconstructive procedure aiming to achieve a flat bone architecture by means of osteoplasty. (a) frontal image during diagnosis and (b) intra-operative frontal image

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Figures

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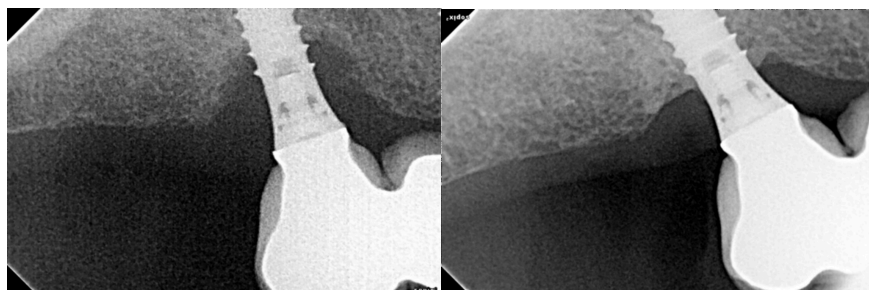

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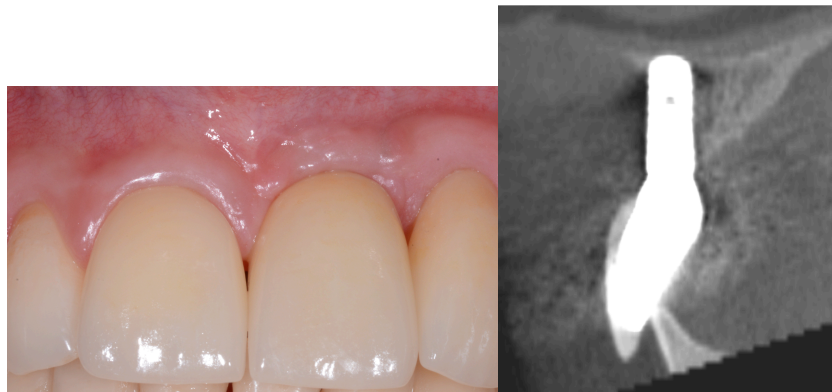

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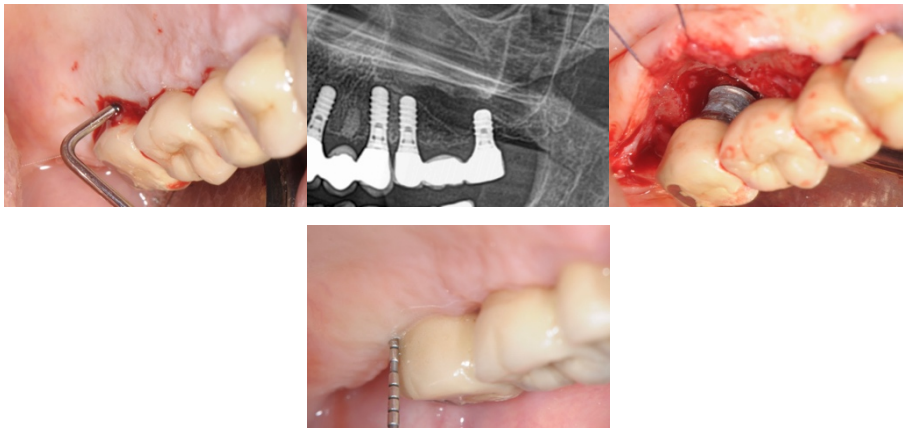

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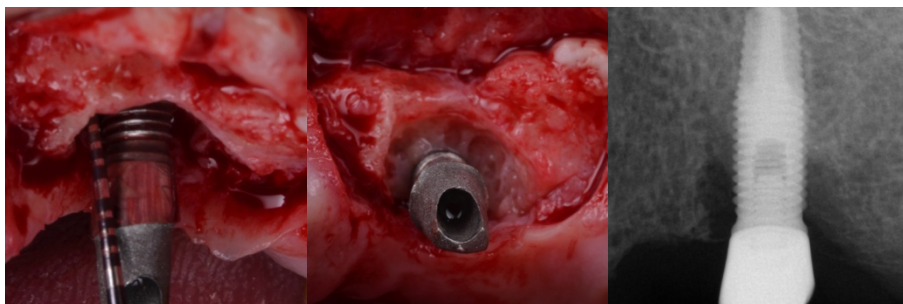

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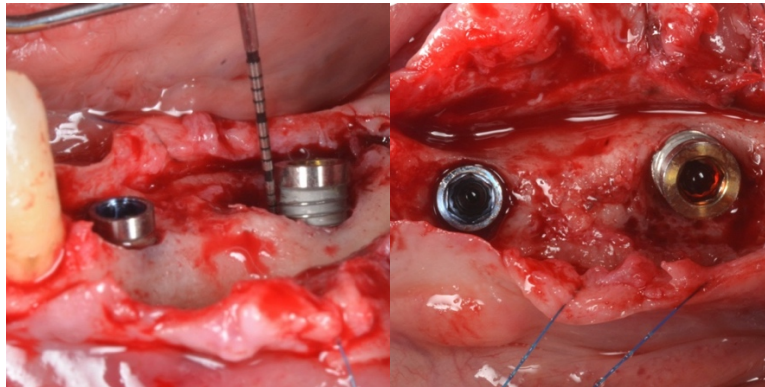

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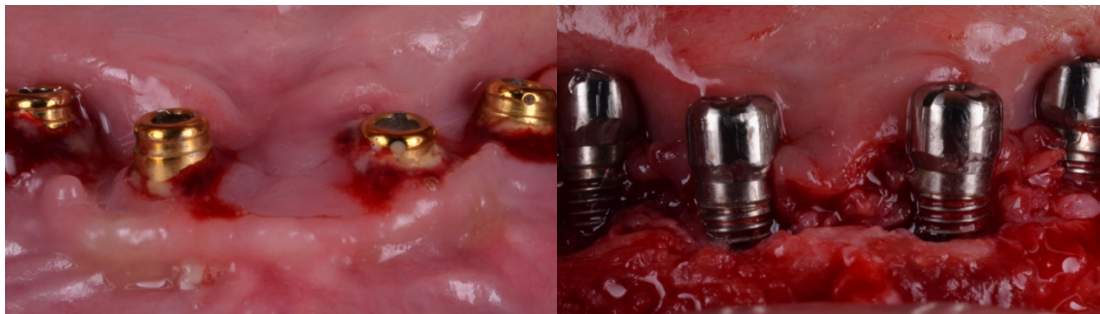

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Trombelli et al. (2020)	Sub-Periosteal Peri-Implant Augmented Layer Technique (SPAL). In this technique a split-thickness flap is elevated leaving a periosteal layer creating a pouch to stabilize the xenograft. In case of insufficient Keratinized mucosa, a connective tissue graft was placed on the buccal aspect	3 (3)	Treatment resulted into significant reconstruction of the peri-implant support in absence of deep pockets or inflammation
Noelken and Al-Nawas (2020)	Laser-Assisted Peri-implant Defect Regeneration (LAPIDER). Horizontal mucosal incision 5 mm apical to the marginal mucosa, subperiosteal coronal flap elevation, debridement of the implant surface with Er:YAG laser, grafting with particulated autogenous bone + connective tissue.	1 (1)	Marginal Bone Levels (MBLs) improved interproximally, buccally and orally at the 1-year examination. Probing depths and recession decreased significantly, while the facial mucosa thickness improved.
Lee et al. (2021)	Peri-implant Excisional Procedure and Access Surgery (PEAS). After the disconnection of the prostheses, the granulation tissue was removed through a peri-implant circular incision in a similar	1 (1)	The surgical intervention was effective in arresting peri-implantitis as no further bone loss but bone fill was observed over a 2-year period.

	manner to the excisional new attachment procedure (ENAP)		
Cortellini et al. (2021)	Reconstructive approaches for the treatment of peri-implantitis lesions using papilla preservation flaps (PPF) and minimally invasive surgery (MIST; i.e. exposing just 1-2 mm of the defect-associated residual bone crest, avoiding "passing" the papilla and releasing incisions if possible)	21 (21)	Primary wound closure was obtained in 100% of the sites. Significant reduction in BOP and PD was observed. Significant radiographic bone fill was observed and maintained throughout the 5 years of follow-up (≈2.5 mm). No discomfort or problem with daily activities was reported by the patients. Post-operative pain was of low intensity (ranging 10-24 on a 0-100 visual analog scale)

Table 2. Studies evaluating products or devices that may impact upon the invasiveness and morbidity of reconstructive procedures in the treatment peri-implantitis lesions: interventions, number of patients/implants, and summary of main outcomes.

Study	Intervention	N patients (implants)	Outcomes
Froum et al. (2012)	Regenerative approach including surface decontamination, EMD, a combination of PDGF with DBBM or MFDBA, and coverage with a collagen membrane or a subepithelial connective tissue graft	38 (51)	No implant was lost during the follow-up (3 to 7.5 years). PD reduction ranged 3-10 mm. Radiographic bone gain was 3.8 mm in those implants presenting a visible interproximal defect at the baseline examination. Bone sounding was performed in those cases in which the greatest bone loss was on the facial or oral aspect of the implant, accounting for a 3.0 mm bone gain.
Hamzacebi et al. (2015)	Conventional access flap surgery adding the application of PRF	19 (38)	PRF group demonstrated higher mean PD reduction and more CAL gain after 6 months
Isehed et al. (2016, 2018)	EMD in access flap surgery (RCT)	29 (29)	At the 3-year follow-up visit, 100% of the implants survived in the EMD group, while in the control group survival was 83%. At the 5-year follow-up appointment, survival rates were 85% of the implants in the EMD group vs 75% in the control group.
Isler et al. (2018)	Regenerative approach using DBBM covered either with a CM or CGF (RCT)	52 (52)	Treatment resulted into significant reductions of BOP and PD reduction in both groups at 6 and 12 months without significant differences among groups. Mean defect fill was also not statistically significant different between groups.
Mercado et al. (2018)	Surgical access and debridement, defects filled with a combined mixture of DBBM, EMD and doxycycline powder.	30 (30)	56.6% of the implants were considered successfully treated according to a composite outcome (PD<5 mm, no further bone loss>10%, no BOP/suppuration, no recession>0.5 mm for anterior implants and >1.5 mm for posterior implants) after 36 months
Schlee et al. (2019, 2021)	Regenerative approach with DBBM plus autogenous covered with a CM after decontamination with EC or combination of an EC and a powder spray (RCT)	24 (24)	Mean PD and BOP were significantly reduced, while significant radiographic bone fill was observed 18 months after therapy. No significant differences between groups were observed.
Sun et al. (2021)	Effect of adjunctive PRF to GBR with DBBM and a CM (RCT)	80 (80)	Pain and bleeding were significantly lower 24 hours and 7 days after surgery in the PRF group. Compared with the control group, the PRF group revealed significantly higher regenerated bone density 60 and 120 days after surgery.
Wang et al. (2021)	Effect of adjunctive of Er:YAG laser in the surface decontamination prior to a reconstructive procedure with a mixture of DBBM plus allograft and covered with an acellular dermal matrix membrane (RCT)	24 (NR)	Laser irradiation led to a significantly higher PD reduction 6 months after surgery. No differences were observed for CAL gain or radiographic linear bone gain.

RCT, randomized clinical trial; NR, not reported. EMD, enamel matrix derivative; PDGF, platelet-derived growth factor; DBBM, demineralized bovine bone mineral; MFDBA, mineralized freeze-dried bone allograft; PRF, platelet-rich fibrin; CM, collagen membrane; CGF, concentrated growth factor; EC, decontamination with an electrolytic method; GBR, guided bone regeneration procedures. PD, probing depth; CAL, clinical attachment level; BOP, bleeding on probing.

Table 3. Studies proposing the use of antimicrobial adjuncts to grafting materials in the reconstructive treatment of peri-implantitis: intervention, number of patients/implants and summary of main outcomes.

Study	Intervention	N patients (implants)	Outcomes
Nart et al. (2018)	After mechanical and chemical decontamination, a vancomycin and tobramycin impregnated allograft was placed in the defect and covered with a collagen membrane allowing a non-submerged healing	13 (17)	No implant was lost. Significant reductions in BOP and PD. Mean radiographical intrabony defect filling was 86.7% ± 18.2%
La Monaca et al. (2018)	After mechanical debridement, chemical decontamination using hydrogen peroxide (3%), chlorhexidine (0.2%) and a tetracycline hydrochloride solution was performed before defect filling with mineralized dehydrated bone allograft and a resorbable membrane	34 (34)	At 1-year, no implant showed peri-implant bone loss ≥1.0 mm and 91% of the implants presented absence of PD ≥5 mm and absence of BOP. However, this percentage was 59% at the 5-year examination and 23% of the implants presented bone loss ≥1.0 mm
Gonzalez Regueiro et al. (2021)	Combined approach with implantoplasty of the supraosseous component together with the reconstruction of the intrabony defect using a bone substitute hydrated with a piperacillin/tazobactam 100/12.5 mg solution.	43 (43)	After 12-months 86% of the implants presented disease resolution according to a composite outcome (absence of BOP/suppuration, further bone loss ≤0.5 mm)

BOP, bleeding on probing; PD, probing reduction.