Alberto Monje

Hom-Lay Wang

Unfolding Peri-Implantitis

DIAGNOSIS | PREVENTION | MANAGEMENT

QUINTESSENCE PUBLISHING

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Diagnosis | Prevention | Management

2nd edition

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PREFACE

"Unfolding Peri-Implantitis" is a timely publication to enlarge the armamentarium of the implant clinician. When osseointegration was introduced as a therapy for the replacement of the natural dentition by Branemark, it appeared to be a highly predictable procedure if performed under sterile conditions by dentists with a formal surgical background. It was accepted as an appropriate predictable solution for young and middle-aged edentulous patients. No one anticipated the positive results and the acceptability of clientele to follow through with these therapies.

The treatment regime progressed from edentulous to the partially dentate to the replacement of a single tooth. The satisfaction of the patient continues to focus on the esthetic demands, extending to subgingival placement of prosthetic restorations. There are two categories of patients: a young individual with no exhibition of susceptibility to inflammation presenting with the loss of one tooth. The second category includes periodontally-compromised patients who clearly are susceptible to inflammation. It is universally accepted that there is not one etiology or one common solution for periimplantitis. This timely publication presents an understanding of the disease based on the diagnostic tools that are available.

The corrective activities obviously would be best provided by an early diagnosis. At this point, it would be referred to as mucositis and very likely be corrected by non-surgical methods. However, the prime dictate factor for the future of an implant infected by periimplantitis will be the supporting bone for the implant. The response of all therapies would include the efforts of the patient, the surgeon, and the oral hygienist. This is especially true for those susceptible to inflammation and we must provide a well-constructed maintenance program with a periodicity of about 3 months.

The editors have engaged surgical and prosthetic thought leaders to share their methods ranging from prevention to regeneration. The surgical complications require a decision whether to save a tooth or insert an implant. The location of the implant is important if it can be performed in an acceptable fashion for the patient. The patient's satisfaction will vary greatly from posterior teeth to the esthetic zone. Therefore, there are times where you can save the implant although it is not in the best interest of the patient.

A well-prepared clinician resolves this decision based on previous experience and recently-approved therapeutics. This text provides contemporary information to practice constructive endpoint goals for the patients. I would suggest that there is a place in every dental operatory for this text and I am sure that it will provide the solutions required to manage periimplantitis.

Myron Nevins, DDS

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Dr. Alberto Monje obtained the certificate and Masters in Periodontology from the University of Michigan, Department of Periodontics and Oral Medicine. Since them, he is certified by the American Board of Periodontics. He was the recipient of the ITI Scholarship for 2016-2017 at the University of Bern (Switzerland). Dr. Alberto Monje is PhD in the field of alveolar bone architecture granted by the University of Granada (Spain). He holds a private practice exclusive in Periodontics and Implant Dentistry (CICOM Periodoncia). He is Adjunct Professor at the Department of Periodontics of the Universitat Internacional de Catalunya (Barcelona, Spain), and Assistant Clinical Professor at the Department of Periodontics and Oral Medicine at the University of Michigan (Ann Arbor, USA). Dr. Monje is Visiting Professor at the Department of Periodontology of the University of Bern (Switzerland).

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ACKNOWLEDGEMENTS

Alberto Monje

My family deserves my deepest appreciation, for the understanding and encouragement shown. Without the principles inspired by my parents, the kindness of my wife and the smile of my daughter Miranda, this book would never have been possible. Thank you for giving so much without asking anything in return.

I wish this work to be a tribute to my mentor, Hom-Lay Wang, in recognition of his trajectory, energy and dedication. You have always been a source of inspiration for me and for all your students. Thank you for always being there, boss.

Hom-Lay Wang

The completion of this textbook is the result of a tremendous amount of work and support from all those involved. First, I would like to thank my co-editor, Alberto Monje, for his friendship and the contribution to this important book.

Second, I would also like to thank and express my gratitude for the unconditional support from my research collaborators, mentors, former and current students, University of Michigan staff, and the chairs of the Department of Periodontics. And lastly, I wanted to dedicate this book to my father and mother, both of whom recently passed away. Without their unselfish love and dedication towards to my education, this would not have been possible.

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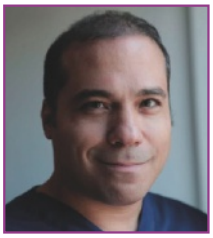

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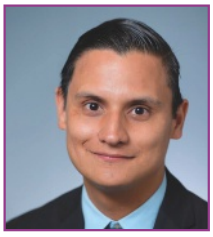

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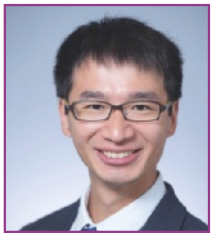

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CHAPTER 4

Pablo Galindo-Moreno, Miguel Padial-Molina, and Francisco J. O'Valle Ravassa

MORPHOLOGIC AND PHENOTYPICAL CHARACTERISTICS OF PERI-IMPLANTITIS

ABSTRACT

Periodontal and peri-implant diseases share a number of common factors, both etiologically and in terms of clinical course. However, key structural differences determine fundamental disparities in their morphologic and phenotypical characteristics. As these may influence the clinical presentation and potential response to treatment, the study of such features should lead to a specific description of what determines such differences. To date, no consensus has been presented in the literature. A potential explanation might be the fact that implant systems, prostheses, and location in the oral cavity are all variables that could influence the presentation of the disease; however, this has not been yet analyzed in detail. This chapter aims to describe the current understanding of the morphologic and phenotypical characteristics of peri-implantitis in an effort to promote better understanding of the disease.

LEARNING OBJECTIVES FOR THIS CHAPTER

- To assess the structural differences between the periodontium and the peri-implant tissues in health.
- To identify the etiologic factors that drive the inflammatory response around peri-implant tissues.
- To describe the morphologic differences between periodontal and peri-implant diseases.
- To describe the immunophenotypical differences between periodontal and peri-implant diseases.
- To recognize the factors that make it difficult to establish a clear description of the histologic characteristics of the disease.

1. Introduction

Periodontal and peri-implant diseases are inflammatory diseases often described as similar pathologies with common pathogenesis and features.[1] First, similar etiology is identified for both diseases, ie, the presence of pathogenic bacteria.[2] Thus, therapeutic efforts should also be the same. Second, the sequence of events that both disease courses follow is also similar. Both are initiated by an inflammatory response around the sulcus in the form of mucositis or gingivitis that evolves and progresses to affect the underlying bone in the form of peri-implantitis or periodontitis. Third, both diseases share risk factors; in fact, patient history of periodontal disease is known to be associated with an increased susceptibility to peri-implant disease.[3] However, there is an important difference between the disease entities that requires consideration: the pattern of progression of the diseases is highly different, with peri-implantitis lesions progressing more rapidly than periodontal lesions. Several systematic studies have found that the association between a history of periodontal disease and the risk of peri-implantitis (evaluated as increased marginal bone loss) is much higher in the form of the periodontal disease formerly known as *aggressive*,[4-6] in which the alteration of the host response plays a more determinant role than the microbiologic challenge.

The first explanation of the difference in disease progression could be the obvious differences between the tissues surrounding teeth and implants (Table 1). These structural differences, as reproduced, are key to explaining differences in terms of homeostasis and disease pathogenesis. As a consequence, periodontal and peri-implant diseases should be assumed to have different risk factors, causes, initiation, progression, and resolution. These obvious anatomical and functional differences between the tissues leads to differences in the microbiomes of the conditions.[7] In fact, it has been clearly demonstrated that the microbiota in teeth and implants are clearly different, regardless of whether they are affected by disease and their proximity to each other: only 8% of the species are shared between teeth and implants in more than 85% of patients.[8] Interestingly, Cecchinato et al have found that marginal bone loss is an independent phenomenon in teeth and adjacent implants,[9] unaffected by interproximal proximity.[10,11] Moreover, recent studies have found independent progression of marginal bone loss in implants and teeth in patients with uncontrolled periodontal disease.[12]

A key difference between teeth and implants that can potentially explain these differences in microbiota and disease progression is the presence of a gap between the implant and its prosthetic rehabilitation. As demonstrated by Piattelli et al,[13] the presence of this gap is key for the induction of an inflammatory area around it. If the gap is placed away from the bone, using strategies such as platform switching and higher transmucosal abutments, the inflammation can also be separated from the bone, and thus marginal bone loss can be reduced, as abundant evidence has confirmed.[14–21]

Based on these findings, it might be thought that the reaction of periodontal and peri-implant tissues must also be different based on their different anatomical structures and potentials, which would mean the histologic characteristics of the inflammatory processes would also be different.

Table 1. *Structural differences between periodontal and peri-implant tissues*

Tooth-supporting structures	Peri-implant tissues
Cementum	Metallic implant surface
Periodontal ligament	Bone-to-implant contact
Alveolar bone lamina dura	
—	Implant-prosthesis gap
Dentogingival periodontal fibers	Circumferential fibers
Junctional epithelium	Epithelial adhesion
Gingival sulcus	Peri-implant sulcus
Rich blood supply and innervation	Lack of independent vascularization

2. Histologic characteristics of peri-implantitis versus periodontitis

If the periodontium and the peri-implant tissues are structurally different, are colonized by different microbes, and are enriched with different biomarkers and pro- and anti-inflammatory cytokines, the initial logical conclusion is that the cells responsible for the initiation, establishment, and progression of the disease must also be different and behave in distinct ways.

In fact, Berglundh et al established in 2011 what became the consensus from the European Workshop on Periodontology.[22] In that review, it was concluded that although clinically the lesions might share several similarities, periodontal and peri-implantitis lesions can be structurally differentiated. Table 2 presents a summary of the evidence describing the morphologic features of peri-implantitis on its own and in comparison with periodontitis.

Table 2. *Evidence of morphologic features of peri-implantitis versus periodontitis*

References	Number of patients/ implants	Case definition	Time in function	Implant system	Results
Sanz et al (1991)[23]	6 PI patients	PD >3 mm, BOP+, no implant mobility (Periotest <+9), MBL >3 mm, peri-implant radiolucency	At least 1 year	Brånemark	SE: proliferation, acanthosis, and papillomatosis; enlarged intercellular spaces; transmigrating mono- and polymorphonuclear cells ICT occupied 65.5% of the CT compartment ICT: mononuclear and plasma cells dominating, few PMNs, enlarged blood vessels
Cornelini et al (2001)[24]	10 PI patients	PD >5 mm, BOP+, suppuration, swelling, RBL	At least 1 year	ITI implants	ICT: lymphocytes and plasma cells, few neutrophils
Gualini and Berglundh (2003)[25]	6 PI patients	Suppuration, BOP+, no mobility, continuous MBL in radiographs	5–11 years	Brånemark	Ulcerated PE
Bullon et al (2004)[26]	5 CP patients	Sites with PD = 6 mm	NA	NA	Multi-layered parakeratinized OE Langerhans cells and immature dendritic cells in both Granulation tissue, focal hemosiderin, B and T lymphocytes (T cells predominant), macrophages, plasma cells similar in ICT
	5 PI patients/5 implants	PD >5 mm, BOP+, swelling, plaque index 2, RBL	Several months	NR	Multi-layered parakeratinized OE Langerhans cells and immature dendritic cells in both Thin, non-keratinized, partly ulcerated JE Granulation tissue, focal hemosiderin, B and T lymphocytes (T cells predominant), macrophages, plasma cells similar in ICT
Berglundh et al (2004)[27]	6 PI patients/12 implants	Suppuration, swelling and/or fistula, advanced RBL, mobility	4–21 years	Brånemark	PE: rete ridges, apically thin and ulcerated ICT: occupies almost entire CT and reaches apical of the PE, with large numbers of collagen fibers, lymphocytes, and plasma cells and numerous small vessels in the marginal part, while few or absent collagen fibers, few large vascular units, large numbers of plasma cells and PMNs in the central part of the ICT

Table 2. *Evidence of morphologic features of peri-implantitis versus periodontitis (cont.)*

References	Number of patients/ implants	Case definition	Time in function	Implant system	Results
Carcuac and Berglundh (2014)[28]	40 CP patients	Bone loss ≥50% and PD ≥7 mm with BOP at ≥4 teeth	NA	NA	Lesion within a well-defined compartment of CT walled off by a PE toward the pocket and a non-ICT portion on its lateral and apical aspects
	40 PI patients	≥1 implant with peri-implant bone loss ≥3 mm and a peri-implant PD ≥7 mm, with BOP and/or suppuration	2–10 years	Not specified	ICT occupies a considerably larger portion of the CT adjacent to an ulcerated PE and extends apical to the PE, not surrounded by a zone of non-ICT Larger ICT area
Konermann et al (2016)[29]	2 HG patients	NA	NA	NA	NA
	2 HPI patients		1–60 months	Not specified	Subepithelial infiltrates with abundant plasma cells below wide OE and thin PE, partly ulcerated; thin vessels but with thickened walls and perivascular hyalinization; and frequent bone fragments
	21 PI patients	BOP, PD >4 mm and loss of attachment level >3 mm			
Galindo-Moreno et al (2017)[30]	15 CP patients	≥4 teeth with ≥1 site with PD ≥4.0 mm and CA loss ≥3.0 mm, BOP	NA	NA	Similar non-ulcerated vestibular epithelium, lamina propria with reduced area of CT, moderate to severe lymphocytes, and a predominantly plasma cell inflammatory infiltrate with numerous monocytes/macrophages but fewer neutrophil granulocytes, mainly near the PE Higher bacterial colonies
	15 PI patients	PD >5.0 mm, BOP, RBL of >3.0 mm	≥1 years	Implant type not specified Screw-retained crowns	Non-ulcerated vestibular epithelium, lamina propria with reduced area of CT, moderate to severe lymphocytes, and a predominantly plasma cell inflammatory infiltrate with numerous monocytes/macrophages but fewer neutrophil granulocytes, mainly near the PE Multinucleate cells near the PE in only one case Inflammatory infiltrate significantly more severe and significantly higher proportion of plasma cells

Table 2. *Evidence of morphologic features of peri-implantitis versus periodontitis (cont.)*

References	Number of patients/ implants	Case definition	Time in function	Implant system	Results
Karatas et al (2020)[31]	15 HG patients	NA	NA	NA	Significantly higher fibroblast density in periodontal health followed by PIM, periodontitis and PI
	15 CP patients	Stage 3 grade B periodontitis			
	15 PIM patients	Peri-implant diseases consensus of 2017	NR	NR	Similar inflammatory cell density in periodontitis and PI
	15 PI patients				
Galárraga-Vinueza et al (2020)[32]	4 patients/5 implants	BOP with or without suppuration, PD ≥6 mm, and RBL ≥3 mm	12 ± 6 years in function	Machined implants supporting screw-retained single prostheses	Osteocyte lacunae with similar signs of stained osteocytes and with no viable cells Two specimens with mixed chronic inflammatory infiltrate, one presented osteoclastic activity, three inactive crestal bone surfaces, and one active bone formation Residual bone predominantly cortical with few vascular channels and signs of compaction of old cancellous bone; frequent secondary osteons and reversal lines

BOP, bleeding on probing; CA, clinical attachment; CP, chronic periodontitis; CT, connective tissue; HG, healthy gingiva; HPI, healthy peri-implant mucosa; ICT, infiltrated connective tissue; JE, junctional epithelium; MBL, marginal bone loss; NA, not applicable; NR, not reported; OE, oral epithelium; PE, pocket epithelium; PI, peri-implantitis; PIM, peri-implant mucositis; PMN, polymorphonuclear neutrophils; PD: probing depth; RBL, radiographic bone loss; SE, sulcular epithelium.

Summary of findings

Limited human evidence suggests that peri-implantitis displays lesions that are not well defined and have more infiltrated connective tissue compared with periodontitis lesions. Moreover, supporting bone at peri-implantitis sites seems to be predominantly cortical with signs of compaction of old cancellous bone.

In summary, both diseases can be morphologically differentiated by some critical histopathologic parameters:

- Both periodontitis and peri-implantitis present large areas of infiltrated connective tissue (ICT) lateral to the pocket epithelium.
- The ICT in peri-implantitis extends more apically than in periodontitis.
- Although plasma cells and lymphocytes are found similarly in both diseases, peri-implantitis lesions present higher relative proportions of macrophages and neutrophil granulocytes. The latter are usually located far from the pocket in peri-implantitis.
- In peri-implantitis, the ICT is usually uncovered and exposed to the pocket area.

However, a study involving the analysis of periodontitis and peri-implantitis lesions by three independent specialized pathologists found similar percentage and distribution of inflammatory cells in periodontitis and peri-implantitis. Intra- and interexaminer agreement in distinguishing blinded biopsies from both diseases were poor, which confirms that the criteria described above is not completely valid.[30] Based on this, it can be concluded that periodontitis and peri-implantitis cannot be truly differentiated based only on morphologic features (Figs 1 to 4).

3. Immunophenotypical characteristics of peri-implantitis versus periodontitis

In order to properly identify differences between the two diseases, structural and morphologic differences must be accompanied by immunophenotypical analyses, including immunohistochemical (IHC) techniques or similar. Table 3 summarizes evidence describing immunophenotypical features of peri-implantitis on its own or in comparison with periodontitis. Acronyms of IHC markers are specified in Table 4.

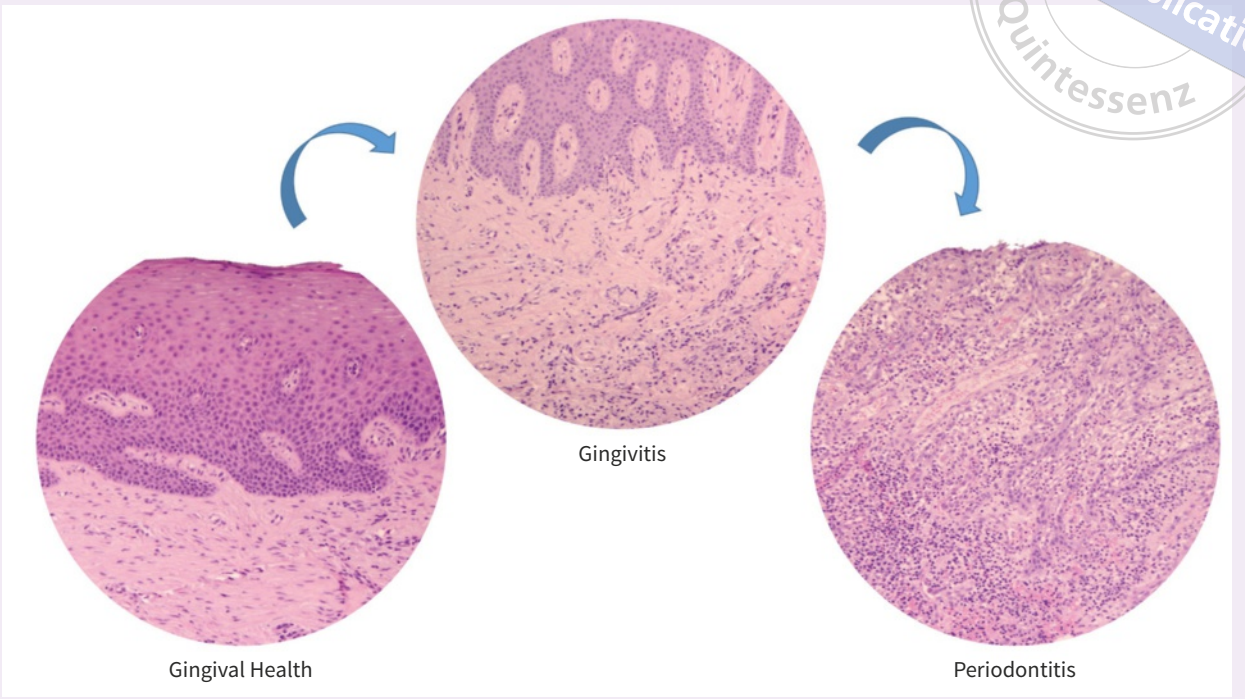

Fig 1. *Histologic features of healthy periodontal mucosa, gingivitis, and periodontitis lesions (hematoxylin & eosin [H&E] stain). Magnification: 10x.*

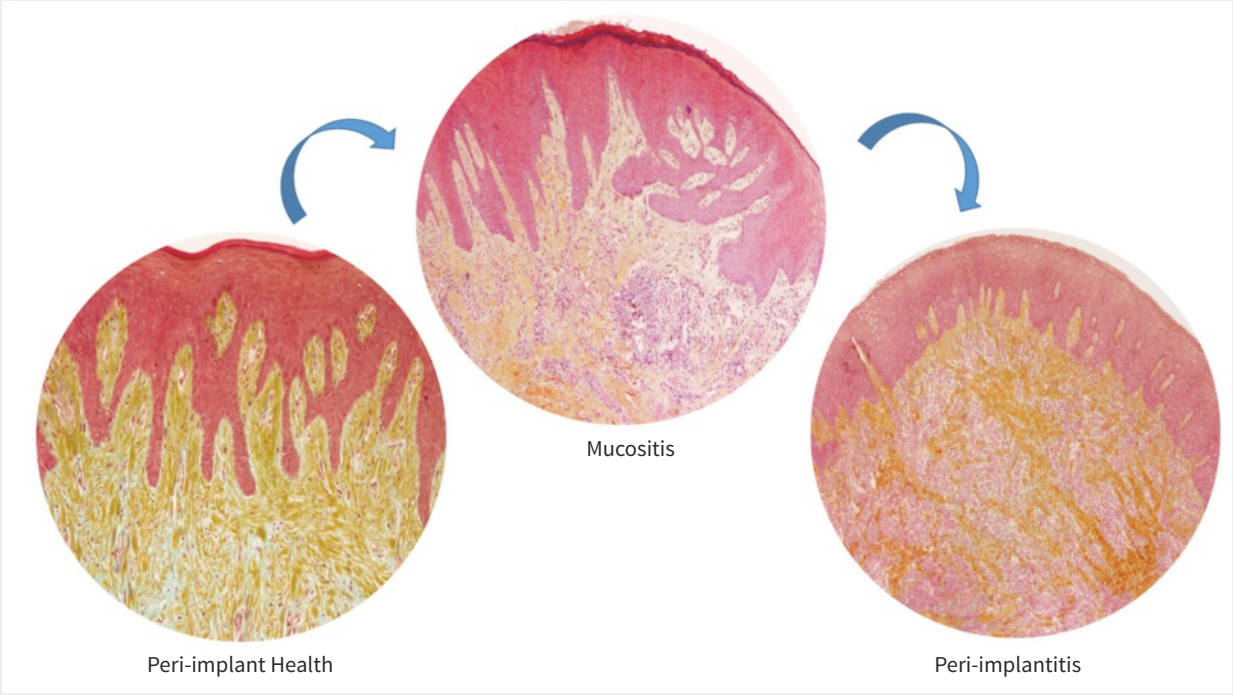

Fig 2. *Histologic features of healthy peri-implant mucosa, mucositis, and peri-implantitis lesions (Movat pentachrome stain). Magnification: 10x.*

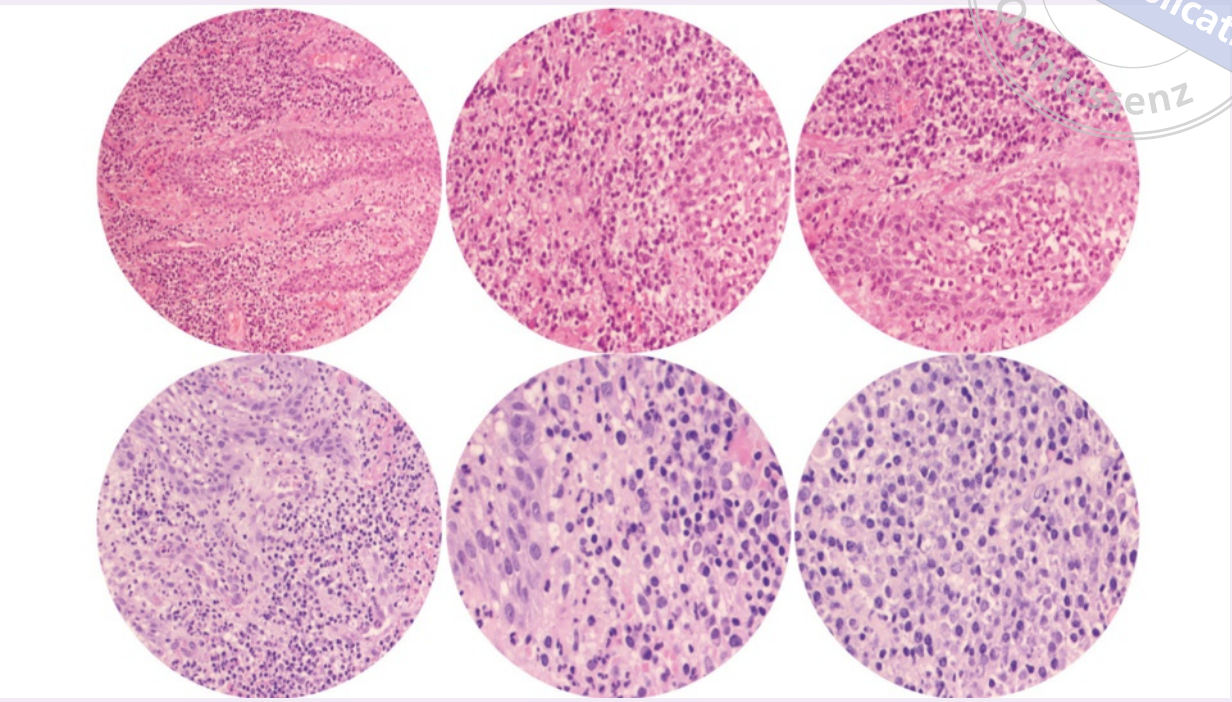

Fig 3. *Representative microphotographs of severe chronic periodontitis. Note the predominance of plasma cells in the inflammatory infiltrate of the lamina propria and the neutrophil exocytosis in the sulcular epithelium (H&E stain). Magnification: 4x-20x.*

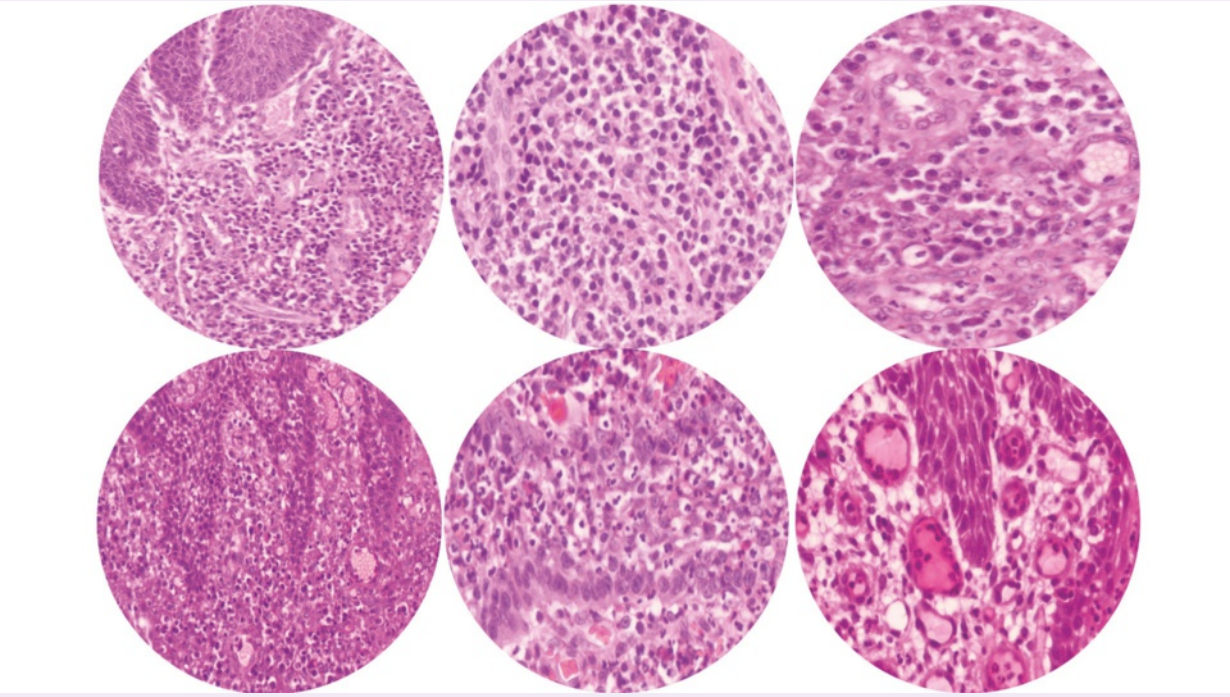

Fig 4. *Representative microphotographs of the similar morphologic features between a case of severe peri-implantitis and those observed in a chronic periodontitis biopsy (H&E stain). Top row: periodontitis, bottow row: peri-implantitis. Magnification: 10x.*

Table 3. *Evidence of immunophenotypical features of peri-implantitis versus periodontitis*

References	Number of patients/ implants	Case definition	Time in function	Implant system	IHC markers	Results
Cornelini et al (2001)[24]	10 PI patients	PD >5 mm, BOP+, suppuration, swelling, RBL	1 year	ITI implants	VEGF and MVD	All vessels and most lymphocytes and neutrophils were VEGF positive
Gualini and Berglundh (2003)[25]	6 PI patients	Suppuration, BOP+, no mobility, continuous MBL in radiographs	5–11 years	Brånemark	CD3, CD4, CD8, CD19, elastase	Lateral to the PE: elastase-positive cells ICT: large proportions of B cells (CD19+) and elastase-positive cells; B cells outnumbered T cells (CD3: 10%; CD4: 8%; CD8: 6%; CD19: 13%; elastase: 4%)
Bullon et al (2004)[26]	5 AG patients	PD = 6 mm	NA	NA	CD1a, CD34, factor VIII, VEGF, and oncoproteins bcl2 and p53	Similar bcl2 and p53
	5 PI patients	PD >5 mm, BOP+, swelling, plaque index 2, RBL	Several months	Not specified		Similar bcl2 and p53 Multi-layered parakeratinized OE with less CD1a and CD34, but more VEGF and bcl2 More CD34, factor VIII, and VEGF
Konttinen et al (2006)[33]	10 HG patients	NA	NA	NA	TNF-α, IL-1α, IL-6, PDGF-A, TGF-α	NA
	10 CP patients	NR				NA
	10 PI patients	Pain during mastication and implant mobility and vertical bone loss	NR	NR		Higher percentage of IL-1α and IL-6 and lower percentage of TNF-α Foreign body giant cells
Carcuac and Berglundh (2014)[28]	40 severe CP patients	Bone loss ≥50% and PD ≥7 mm with BOP at ≥4 teeth	NA	NA	CD3, CD20, CD34, CD68, CD138 and MPO	Higher CD3, CD20, and vascular units within the ICT
	40 PI patients	≥1 implant with MBL ≥3 mm and PD ≥7 mm, BOP and/or suppuration	2–10 years	Not specified		Higher CD138, CD68, MPO, and vascular units lateral to the ICT

Table 3. *Evidence of immunophenotypical features of peri-implantitis versus periodontitis (cont.)*

References	Number of patients/ implants	Case definition	Time in function	Implant system	IHC markers	Results
Konermann et al (2016)[29]	2 HG patients	NA	NA	NA	TRAP, CD3, RANKL, RANK, OPG, and TNF-α	RANKL mainly in suprabasal layers of the epithelium
	2 HPI patients		60 months	NR		NR
	21 PI patients	BOP, PD >4 mm and loss of attachment level >3 mm				Few TRAP+ multinuclear cells located in resorption lacunae Dense or loosely packed clusters of CD3+ cells, intense OPG, and TNF-α Similar RANK staining but different location, mainly in subepithelial lamina propria in PI RANKL mainly in mononuclear cells in infiltrates in PI Correlation between higher RANK and earlier implant loss; higher CD3+ with greater inflammation and in smokers
Galindo-Moreno et al (2017)[30]	15 CP patients	≥4 teeth with ≥1 site with PD ≥4.0 mm and CA loss ≥3.0 mm, BOP	NA	NA	CD34, CD38, CD45, CD68, and MPO	Differences statistically significant only for CD38 and CD34 in the PE
	15 PI patients	PD >5.0 mm, BOP, RBL >3.0 mm	≥1 year	Implant type not specified; screwed-retained crowns		
Karatas et al (2020)[31]	15 HG patients	NA	NA	NA	HIF-1α, PH, MMP-8, TIMP-1, COX-2, and iNOS	HIF-1α: HG < PIM < CP < PI PH: CP < PI < PIM < HG TIMP-1: HG < CP < PI < PIM MMP-8, COX-2, and iNOS: HG < PIM < CP < PI
	15 CP patients	Stage 3 grade B periodontitis				
	15 PIM patients	Peri-implant diseases consensus of 2017	NR	NR		
	15 PI patients					
Fretwurst et al (2020)[34]	7 CP patients	Stage III or IV periodontitis	NA	NA	CD68, iNOS, CD206	Fewer macrophages and less polarization Higher number of M2 than M1
	7 PI patients	BOP and/or suppuration, changes in level of crestal bone with or without concomitant deepening of PD	NR	NR		Balanced proportion of M1 (iNOS+, representative of acute phase) and M2 (CD206, representative of resolution phase) macrophages

AG, aggressive periodontitis; CP, chronic periodontitis; HG, healthy gingiva; HPI, healthy peri-implant mucosa; ICT, infiltrated connective tissue; MBL, marginal bone loss; MVD, microvessel density; NA, not applicable; NR, not reported; OE, oral epithelium; PE, pocket epithelium; PI, peri-implantitis; PIM, peri-implant mucositis; PD, probing pocket depth; BOP, bleeding on probing; CA, clinical attachment; RBL, radiographic bone loss.

Summary of findings

Limited human evidence suggests that peri-implantitis presents as a more acute inflammatory process dominated by neutrophils and plasma cells in contrast to periodontitis. Moreover, peri-implantitis lesions display higher numbers of macrophages displaying a distinct macrophage M1 polarization signature compared to periodontitis lesions (Fig 5).

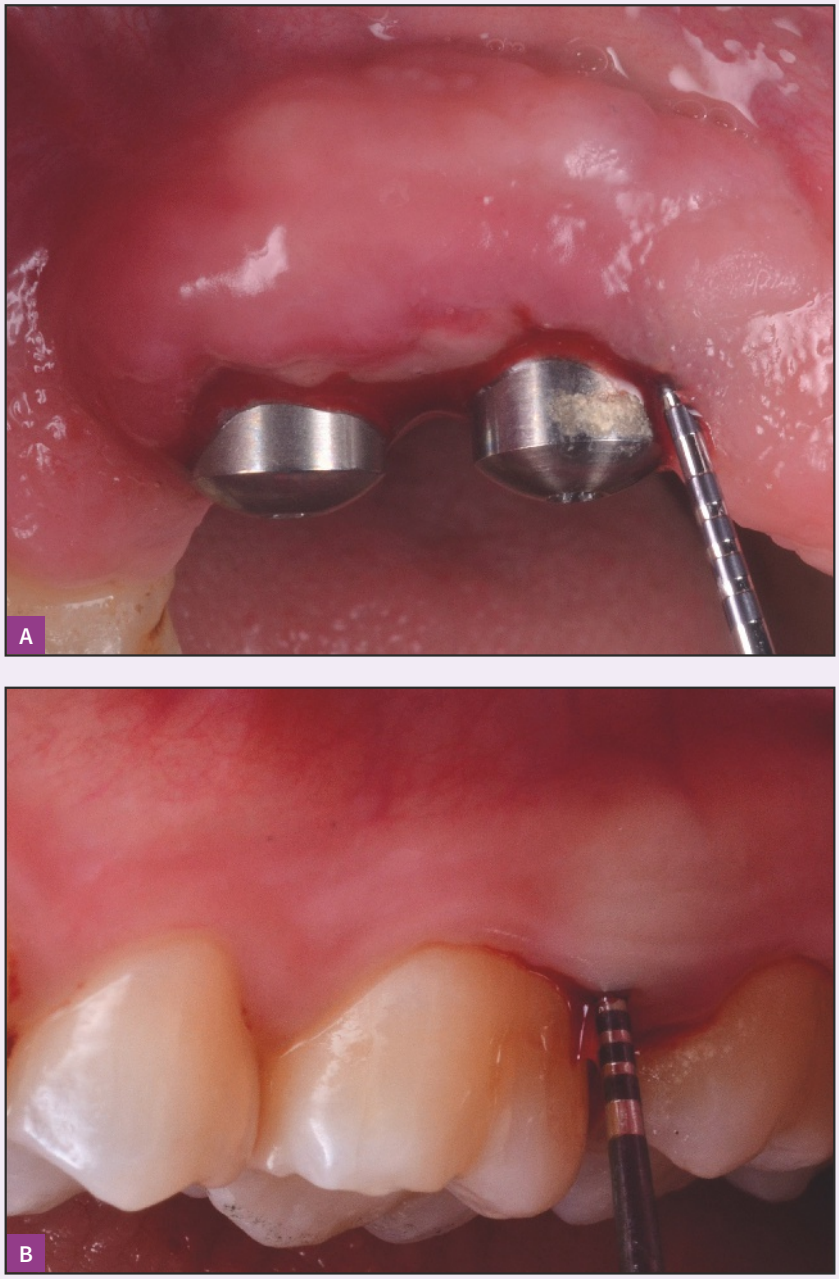

Fig 5 (A and B). *Peri-implantitis lesions display a more aggressive inflammatory course compared to periodontitis lesions. This often leads to more advanced bone loss and poorer prognosis for diseased implants.*

Table 4. *Immunohistochemical markers used in different studies*[35]

Marker	Definition / Relevance
CD1a	Mediates the presentation of self or microbial non-peptide antigens to T cells
CD3	Specific cell surface receptor of cytotoxic T (CD8+) and T-helper (CD4+) cells that mediates their activation
CD4	Surface glycoprotein on T-helper cells, monocytes, macrophages, and dendritic cells that mediates their activation
CD8	Transmembrane glycoprotein that acts as a co-receptor on cytotoxic T, natural killer, cortical thymocytes, and dendritic cells
CD19	Transmembrane protein on pre-B and all B cells except plasma and dendritic cells that regulates their development, activation, and differentiation
CD20	Similar to CD19 but more specific as it is only present on true B cells, from naive to maturity
CD34	Transmembrane phosphoglycoprotein expressed in multiple cell types of blood vessels
CD38	Glycoprotein on the surface of white blood cells that regulates cell activation, proliferation, and adhesion
CD45	Transmembrane protein essential for the regulation of T and B cell antigen receptor signaling
CD68	Expressed in monocytes and circulating and tissue macrophages with a role in their phagocytic activities
CD138	Particularly expressed in plasma cells and pre-B cells and relevant for cell adhesion; also called syndecan
CD206	Expressed in monocytes, macrophages, and Langerhans cells to facilitate endocytosis
COX-2	Prostaglandin-endoperoxide synthase 2 involved in the conversion of arachidonic acid to prostaglandin H2 that mediates responses to infection and inflammation
Elastase	Intervenes in the proteolysis of elastin, an important determinant of the mechanical properties of the connective tissue
Factor VIII	Coagulation factor, also known as anti-hemophilic factor, produced in endothelial cells
HIF-1α	Hypoxia-inducible factor 1-alpha; acts as a transcriptional regulator of the adaptive response to hypoxia, activating the transcription of numerous genes, including VEGF, to increase oxygen delivery
IL-1α	Interleukin 1-alpha; produced by activated macrophages to stimulate B cell maturation and proliferation

Table 4. *Immunohistochemical markers used in different studies[35] (cont.)*

Marker	Definition / Relevance
IL-6	Interleukin 6; inductor of acute phase response, ie, activation of B cell differentiation, but also affects T cells and hematopoietic progenitor cells
iNOS	Inducible nitric oxide synthase; produces nitric oxide that mediates bactericidal actions of macrophages
MMP-8	Matrix metalloproteinase 8 or neutrophil collagenase; degrades fibrillar type I, II, and III collagens
MPO	Myeloperoxidase; expressed in PMN and acts as microbicidal
bcl2	Regulates cell death by controlling mitochondrial membrane permeability
p53	Induces growth arrest or apoptosis and inhibits cell division
OPG	Osteoprotegerin or tumor necrosis factor receptor superfamily member 11B; decoy receptor of RANKL, thus, neutralizes the activation of osteoclasts
PDGF-A	Platelet-derived growth factor subunit A; regulates cell proliferation and migration, thus plays a role in wound healing
PH	Prolyl hydroxylase; degrades HIF-1α
RANK	Receptor activator of nuclear factor-kappa B or tumor necrosis factor receptor superfamily member 11A; essential for osteoclastogenesis
RANKL	Receptor activator of nuclear factor-kappa B ligand or tumor necrosis factor ligand superfamily member 11; essential for osteoclast differentiation and activation as well as the ability of dendritic cells to stimulate naive T cell proliferation
TGF-α	Transforming growth factor alpha; inductor of mitosis
TIMP-1	Metalloproteinase inhibitor 1; inactivates metalloproteinases
TNF-α	Tumor necrosis factor alpha; mainly secreted by macrophages to induce cell death and impair regulatory T cells
TRAP	Tartrate-resistant acid phosphatase; highly expressed in active osteoclasts
VEGF	Vascular endothelial growth factor; stimulates the formation of blood vessels

As summary, peri-implantitis lesions can be immunophenotypically differentiated from periodontitis by:

- Higher number of B and multinucleated cells
- Less vascularization
- Higher indicators of tissue acute inflammatory phase and hypoxia

However, these results have not been confirmed by other studies with similar methodology.[30] Again, even using immunophenotypical characterization, diagnostic agreement was very low at both the intra- and interexaminer levels. Thus, other key parameters must be analyzed in order to properly characterize and elucidate the specific mechanisms that underlie disease pathogenesis.

4. Clinical significance of the morphologic and phenotypical characteristics of peri-implantitis

The clinical relevance of these findings lies in the prognosis of dental implants that have developed marginal bone loss as a consequence of the biofilm-mediated inflammatory process (Fig 6). However, as discussed, it is difficult to establish clear diagnostic criteria and to describe the pathogenesis and natural history of the disease. Possible explanations for the discrepancies are differences in the particular characteristics of the specimens under evaluation across different studies, level of progression of the disease, time since its initiation, etc. Additionally, in recent years, the role of titanium particles released from the implant or the abutment is being explored as a potential inductor of deleterious tissue responses.[36–41] Moreover and related to the latter, each implant system, macro- and microdesign, prosthetic connection, alloy, and so on, must be considered in the future when analyzing the pathogenesis of peri-implant disease. In addition, differences exist between teeth according to their location, but we commonly use the same type of implant regardless of location. This aspect should also be explored and characterized since the mucosa, occlusal forces, and access for hygiene are completely different in each anatomical location.

5. Concluding remarks

Peri-implantitis lesions often exhibit differential morphologic and phenotypical characteristics compared to periodontitis lesions. In particular, it seems that peri-implantitis lesions are generally larger in size, with larger inflammatory cell infiltrates that extend closer to the bone crest, and contain larger proportions of plasma cells and osteoclasts compared to periodontitis lesions. Moreover, peri-implantitis lesions display higher numbers of macrophages demonstrating a distinct macrophage M1 polarization signature compared to periodontitis lesions. These differential features may help in understanding the distinct patterns in the progression of peri-implantitis versus periodontitis lesions.

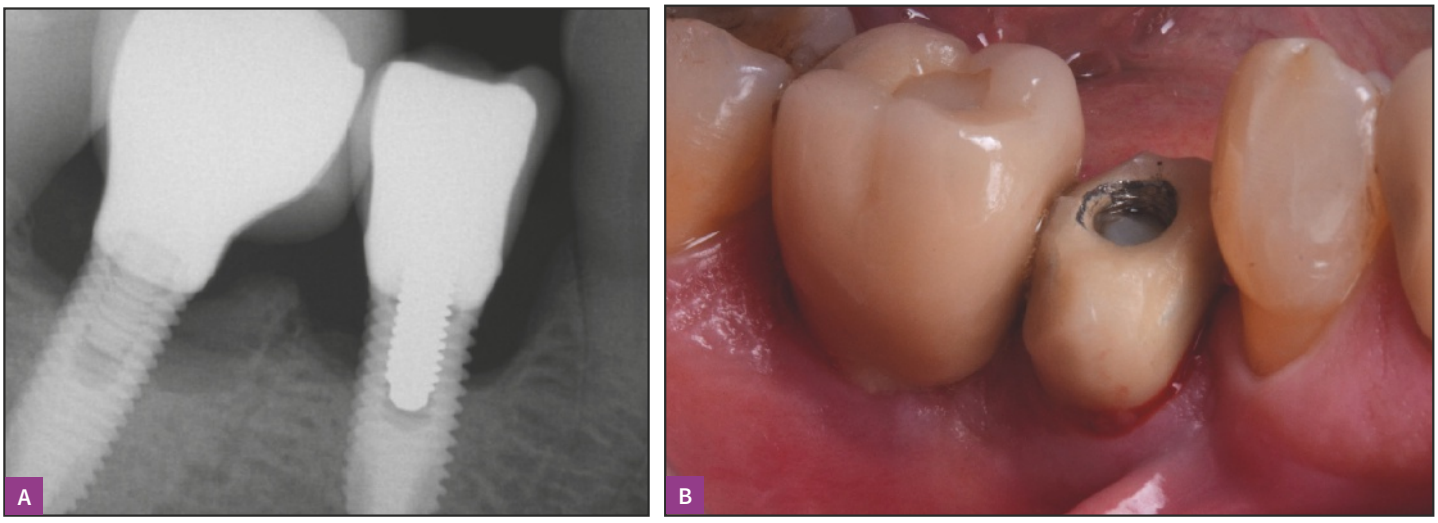

Fig 6 (A and B). *Peri-implantitis lesions are generally larger in size, with larger inflammatory cell infiltrates that extend closer to the bone crest.*

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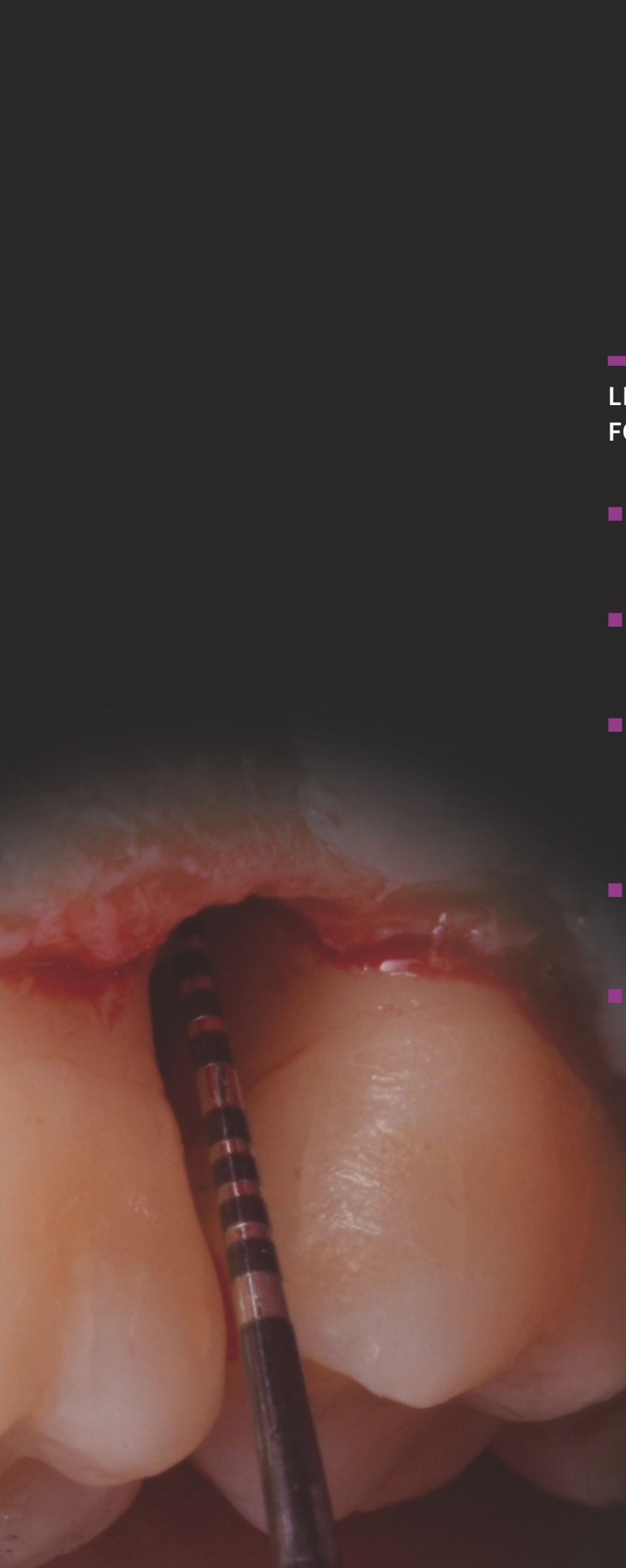
CHAPTER 12

Alberto Monje and Roberto Abundo

MANAGEMENT OF PERI-IMPLANTITIS. PART 1: LESSONS LEARNED FROM THE TREATMENT OF PERIODONTITIS

ABSTRACT

During the last two decades of ceaseless study on the management of peri-implantitis, its predictability and effectiveness have been the subject of controversy. In fact, with the rapid growth in the popularity of implant therapy, there was an unanticipated occurrence of biologic complications and a lack of knowledge regarding how to manage these disorders. In an attempt to arrest the disease, all endeavors have been made to reconstruct lost soft and hard tissue support, often applying empiric treatment modalities. Nonetheless, it is important to note that peri-implant health reestablishment is achieved by reducing pocket depth to ≤5 mm and eliminating inflammation within the soft tissues to arrest progressive bone loss. In fact, a wide variety of features, including patient- and site-related factors, may affect the predictability of the approach. Hence, with the goal of succeeding in the management of these disorders and achieving long-term peri-implant health, the lessons learned in the management of periodontitis over more than a century should be applied to predictably assess the prognosis of and treat peri-implant lesions.



LEARNING OBJECTIVES FOR THIS CHAPTER

- To understand the objectives in the management of periodontitis and peri-implantitis
- To provide therapeutic goals in the management of oral inflammatory diseases
- To provide the possibilities and limitations associated with different therapeutic modalities based on knowledge and understanding applied from the management of periodontitis
- To evaluate the role that defect morphology plays in the treatment of periodontitis and peri-implantitis
- To outline the stages of a treatment plan for management of peri-implantitis according to lessons learned from periodontitis

1. Introduction

Periodontal diseases have been a subject of investigation for more than a century. In fact, historic reports named periodontal disease as pyorrhea alveolaris, Rings disease, calcic pericementitis, interstitial gingivitis, phagedenic pericementitis, or chronic suppurative pericementitis.[1] Regardless of the name, the notion that disease was caused primarily by local irritants such as calculus and pathogenic bacteria and their byproducts was agreed upon by the pioneers in the study of these entities. More recently, study of systemic interactions with other diseases and conditions have absorbed all the attention of researchers.

According to disease progression, age of the patient, and other immunologic and microbiologic features, these disorders were further classified as aggressive or chronic. Nowadays, periodontal diseases are characterized as microbially associated, host-mediated inflammatory conditions that result in the loss of periodontal attachment. With the goal of identifying disease severity and extent, assessing complexity, and estimating future risk and the potential health impact of periodontitis, grading and staging of disease in the diagnostic phase is advocated.[2]

In light of the impact of periodontitis on quality of life and health, endeavors have also been made to study predictable and efficient therapeutic modalities to manage periodontitis. Given that periodontitis (Fig 1), alike peri-implantitis (Fig 2), is an inflammatory condition evoked by plaque biofilm in susceptible hosts, the therapy includes addressing all local and systemic factors, including deleterious habits that might contribute to disease progression. In this sense, it must be considered that periodontal and peri-implant health can be present in reduced periodontal/peri-implant tissues. Hence, the therapeutic modality is to be tailored to the clinical scenario and the patient's needs.

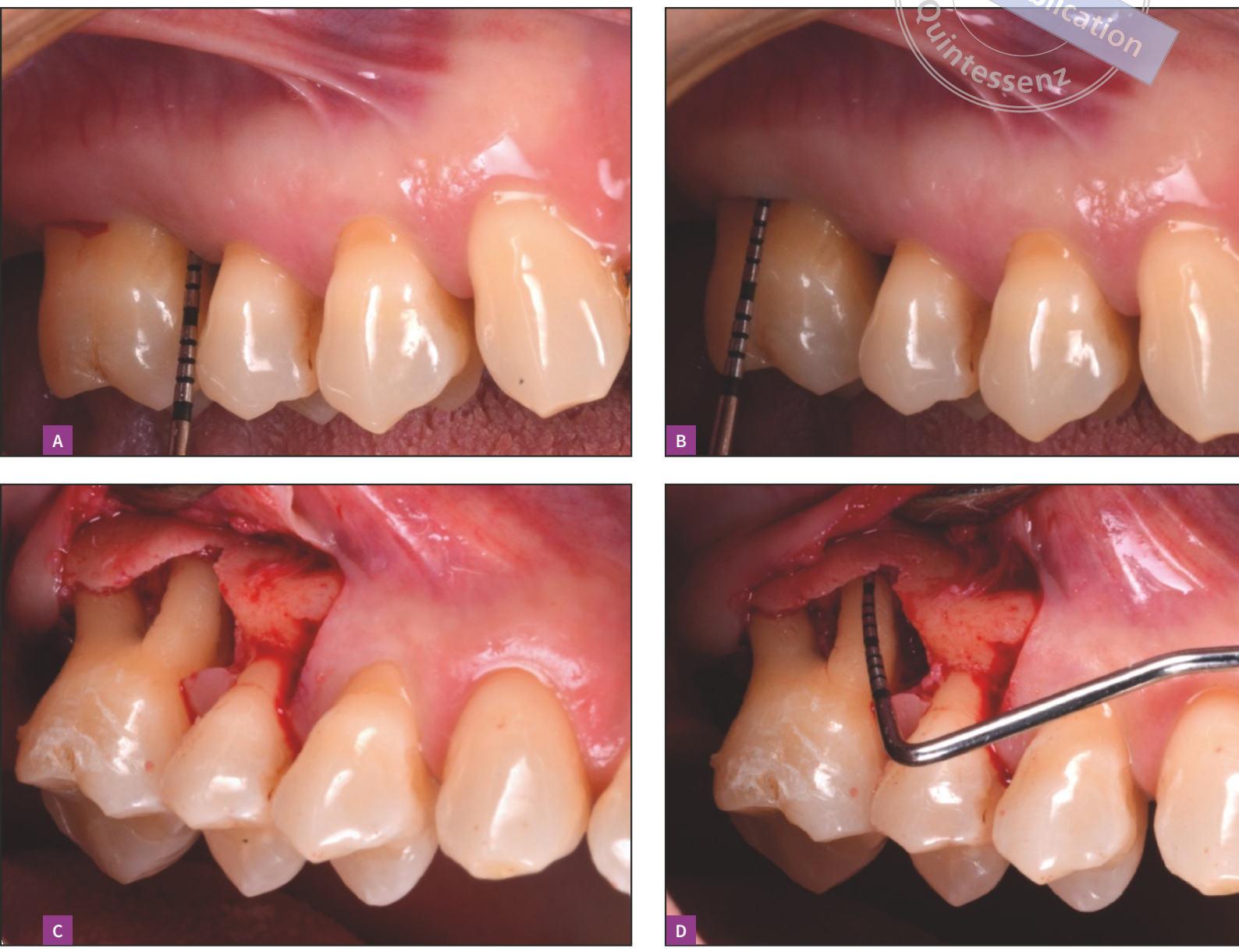


Fig 1 (A to D). *Periodontitis progresses from soft tissue inflammation to the breakdown of the periodontium, including alveolar bone, periodontal ligament, and cementum.*

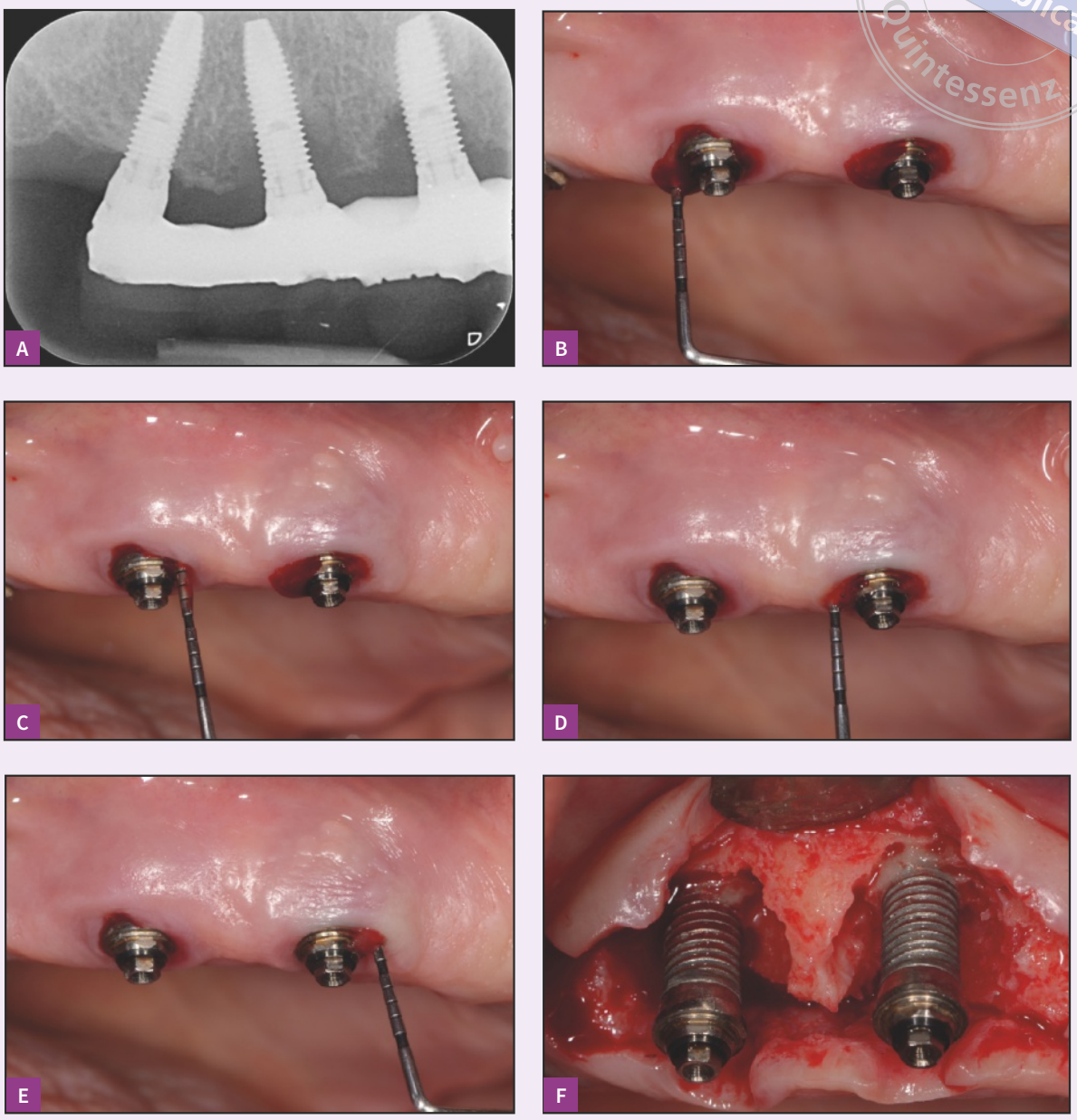


Fig 2 (A to F). *Peri-implantitis progresses from soft tissue inflammation to the breakdown of hard tissues.*

2. Therapeutic goals in the management of oral inflammatory diseases

Given the shared etiologic factors of periodontal and peri-implant diseases, all efforts must be made to remove irritants such as calculus or biofilm that could evoke an inflammatory response (Fig 3). To sustain health and long-term stability, local and systemic factors as well as deleterious habits known increase the pro-inflammatory profile have to be further addressed. Hence, the following therapeutic goals must be fulfilled:

- Identify local and systemic contributors that could interfere with therapeutic outcomes
- Remove etiologic factors
- Provide oral hygiene instructions
- Correct deformities caused by etiologic factors
- Establish healthy habits
- Make teeth/implants biologically acceptable to surrounding tissues
- Establish a primarily aerobic environment
- To the extent possible, provide results that are satisfactory to the patient

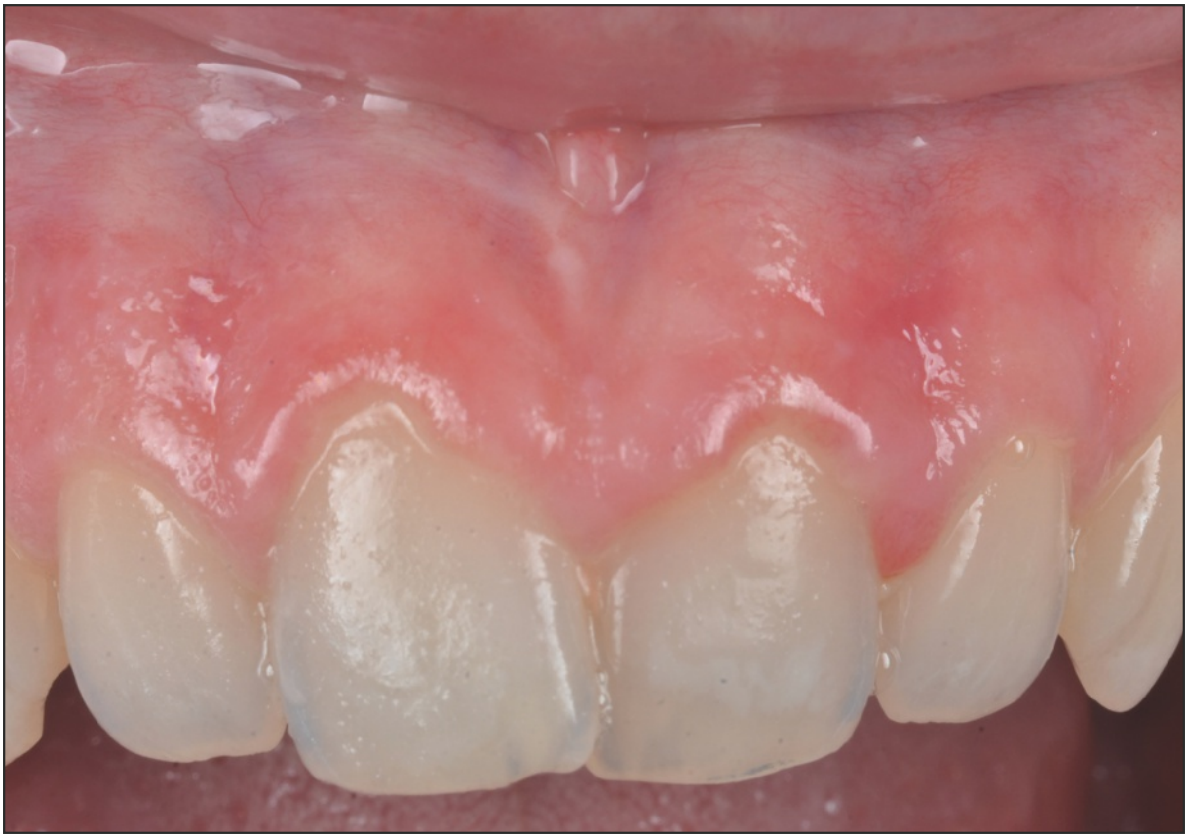


Fig 3. *Periodontal disease is an inflammatory, biofilm-mediated condition that leads to the breakdown of the periodontium and is preceded by inflammation of the soft tissues.*

3. Therapeutic endpoints of success

The following endpoints have to be considered to successfully manage periodontitis and peri-implantitis:

- Reduction of inflammation: bleeding on probing (BOP), erythema, and swelling
- Probing depth (PD) reduction to ≤5 mm
- Arrest of progressive bone loss
- Patient satisfaction

As secondary therapeutic endpoints for procedures encompassing mucogingival deformities, the following endpoints must be considered:

- Increase of gingival/mucosal dimensions
- Root/exposed implant coverage
- Improved patient-reported esthetics

4. Treatment plan: Phases and rationale

The first notion that must be highlighted in the management of periodontal and peri-implant diseases is that there is no "one size fits all." In other words, according to the clinical and radiographic scenario, the treatment plan has to be tailored. Despite the variations in clinical scenarios and functional/esthetic needs, consensus has been reached regarding the stages that have to be included in the treatment plan to provide health in the long term (Table 1).

Table 1. *Phases, therapeutic goals and possible interventions carried out in the management of periodontal and peri-implant disorders*

Phase	Therapeutic goals	Possible intervention
Phase 0	■ Perform problem-oriented history, assessment, and management ■ Eliminate pain/infection	■ Urgent care
Phase I	■ Diagnosis ■ Identify local and systemic contributors ■ Assessment of patient's risk profile ■ Remove etiologic factors by means of non-surgical interventions ■ Instruction and education of oral hygiene measures ■ Establishment of prognosis ■ Reduce and, if possible, eliminate PD and inflammation	■ Clinical and radiographic assessment ■ Non-surgical mechanical intervention ■ Antimicrobial therapy ■ Control of other conditions within the oral cavity ■ Interdisciplinary consult to address modification of local contributors
Reevaluation	■ Re-assessment by clinical means ■ Reinforcement of hygiene habits	■ Clinical assessment
Phase II	■ Correct the sequelae of periodontal/peri-implant disease ■ Achieve visibility to remove etiologic factors ■ Reach a positive or flat bone architecture ■ Eliminate PD associated with pathogenic microbiota and inflammation ■ Condition the soft and hard tissues to promote a healthy environment ■ Reinforcement of hygiene habits	■ Open-flap debridement ■ Bone reconstruction ■ Osseous resective surgery ■ Soft tissue conditioning ■ Implant surface modification
Reevaluation	■ Reassessment by clinical means ■ Reinforcement of hygiene habits	■ Clinical and radiographic assessment
Phase III	■ Supportive maintenance therapy ■ Monitoring ■ Reinforcement of hygiene habits	■ Clinical and if needed radiographic assessment ■ Supra- and subgingival/mucosal detoxification

Phase 0

This phase aims to perform problem-oriented history taking, assessment, and management. Pain and infection should be addressed immediately. It is encouraged to perform a complete clinical and radiographic examination to assess comorbidities (Fig 4).

Phase I: Non-surgical phase

Rationale

Phase I encompasses non-surgical interventions to make teeth and implants biologically acceptable to surrounding tissues by means of mechanically and pharmacologically removing the etiologic factors and arresting disease progression (Fig 5). Also at this stage, instruction and education regarding oral hygiene techniques and healthy habits are administered. In patients presenting with uncontrolled pathologies, medical interdisciplinary consultation must be considered.

In the management of peri-implantitis, it should be noted that a site-specific disorder is often associated with local confounders. Therefore, predisposing factors that do not require surgical intervention (eg, factors related to prosthesis design; see chapter 7) should be addressed.

Significance and effectiveness of non-surgical management of periodontitis

Non-surgical therapy has proved effective to reduce the depth of periodontal pockets and disrupt subgingival microflora, therefore delaying the repopulation of pathogenic microbes and arresting disease progression.[3,4] The Scandinavians first demonstrated that among patients in need of corrective surgical periodontal therapy, those who did not previously undergo non-surgical therapy and exhibited poor plaque control showed more rapid disease progression.[5] This was further demonstrated for patients undergoing a corrective phase for reconstructive purposes.[6] However, this could not be validated at a biomarker level.[7]

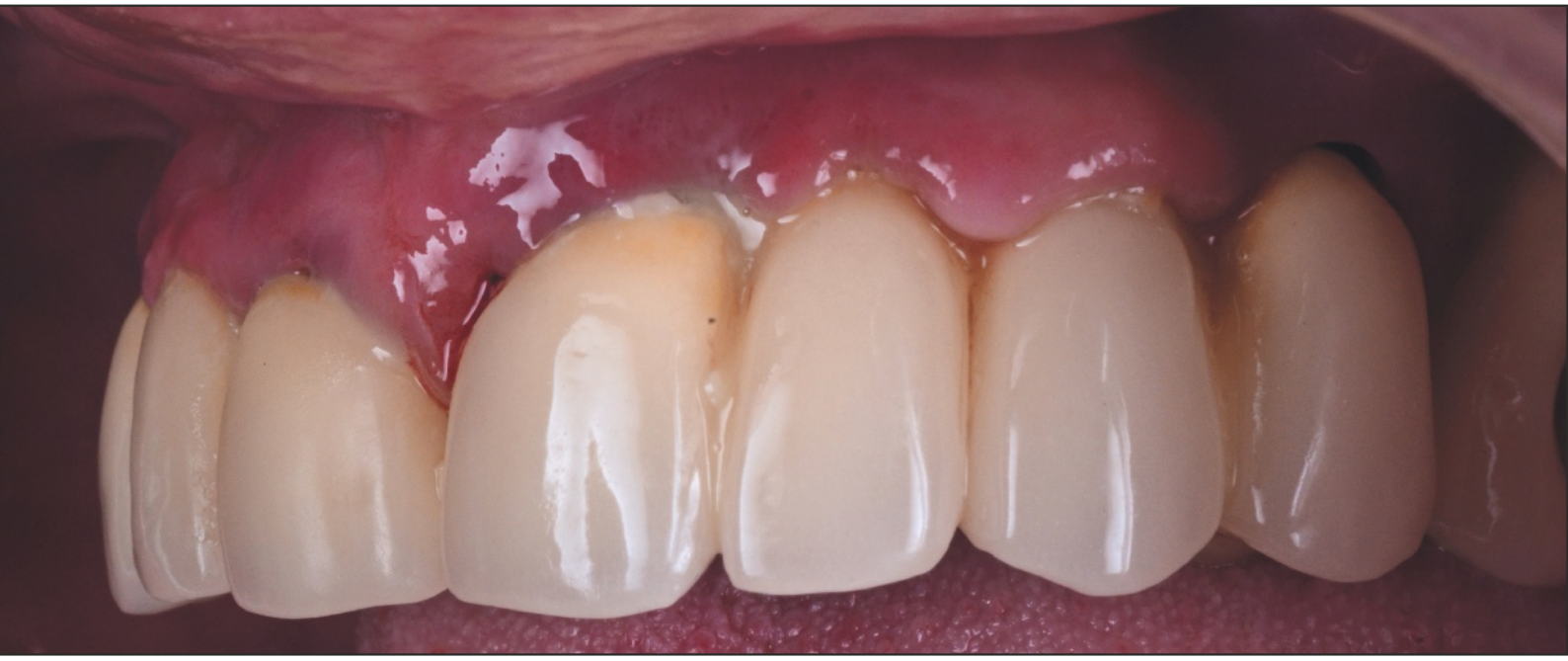


Fig 4. *Patient who presented demanding urgent care for acute pain related to severe peri-implantitis in the maxilla and neck lymphadenopathies. Mechanical instrumentation and antibiotic therapy were applied to control the acute phase of infection.*

Non-surgical therapy, nevertheless, is subject to significant shortcomings. Importantly, when applying non-surgical therapy, visual capacity is limited. This leads to inefficient plaque removal rates at tooth sites.[8] It is worth noting that advances in the designs of curettes and ultrasonic tips may facilitate plaque removal in deep pockets. However, the application of non-surgical therapy at implants sites is further challenged by the complexity of surface detoxification and the retentive nature of implant features such as implant threads.

Non-surgical periodontal therapy by means of scaling and root planing has proven to be highly efficient, in particular for single-rooted teeth[9] and shallow to moderate pocket depths.[10] Longitudinal studies comparing non-surgical mechanical therapy to other surgical therapeutic modalities demonstrated that for shallow PDs (<3 mm), all non-surgical and surgical interventions led to loss of clinical attachment level (CAL). Scaling and root planing are highly effective in moderate PDs (4–6 mm). Nevertheless, for deep PD (>6 mm), surgical access is often required to achieve periodontal health.[11–14] It must be noted that advances such as refinement of minimally invasive approaches using high-magnification devices may enhance the non-surgical outcome in deeper pockets.[15]

The adjunctive use of systemic and local antibiotics has been advocated in the management of periodontitis. The rationale is based on the hypothesis that the inflammatory condition that leads to tissue breakdown is evoked by specific bacteria. Clinical studies have demonstrated limited clinical benefit of using antibiotics as adjuncts to mechanical treatment of periodontitis and low significance of clinical differences in terms of long-term outcomes.[16–19]

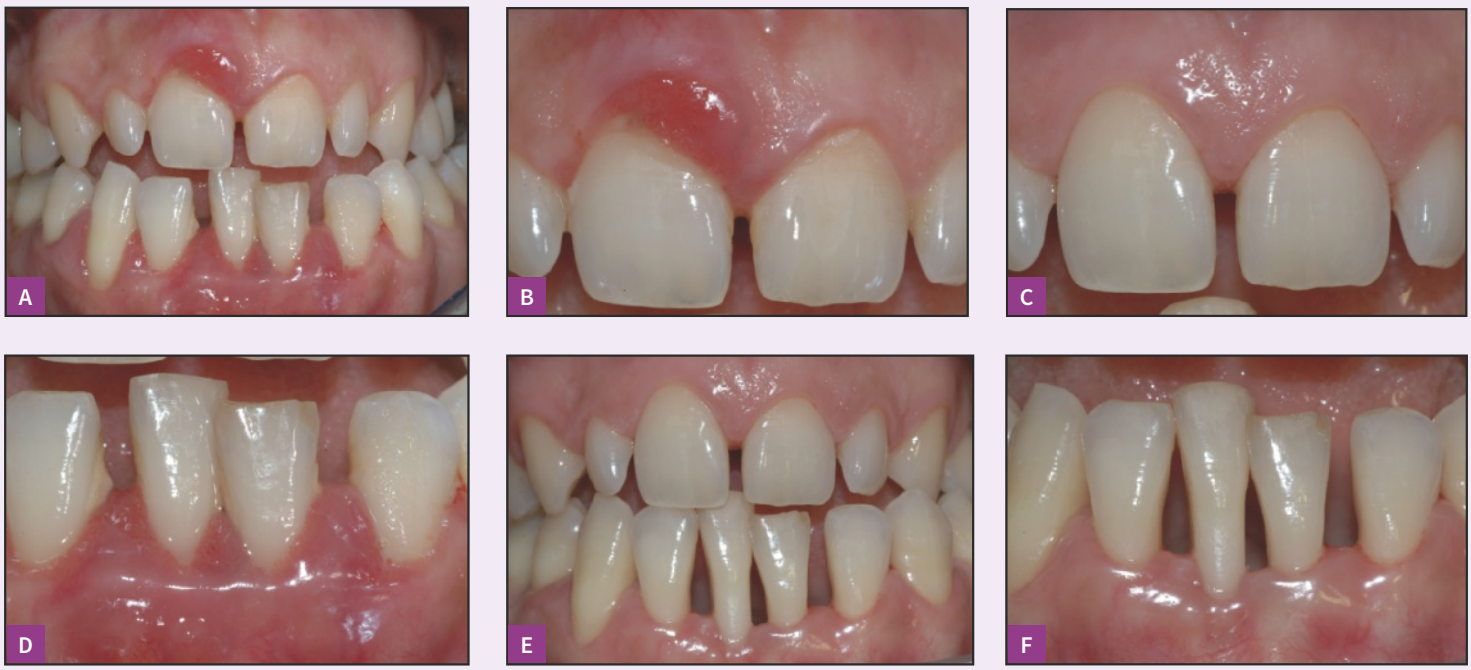
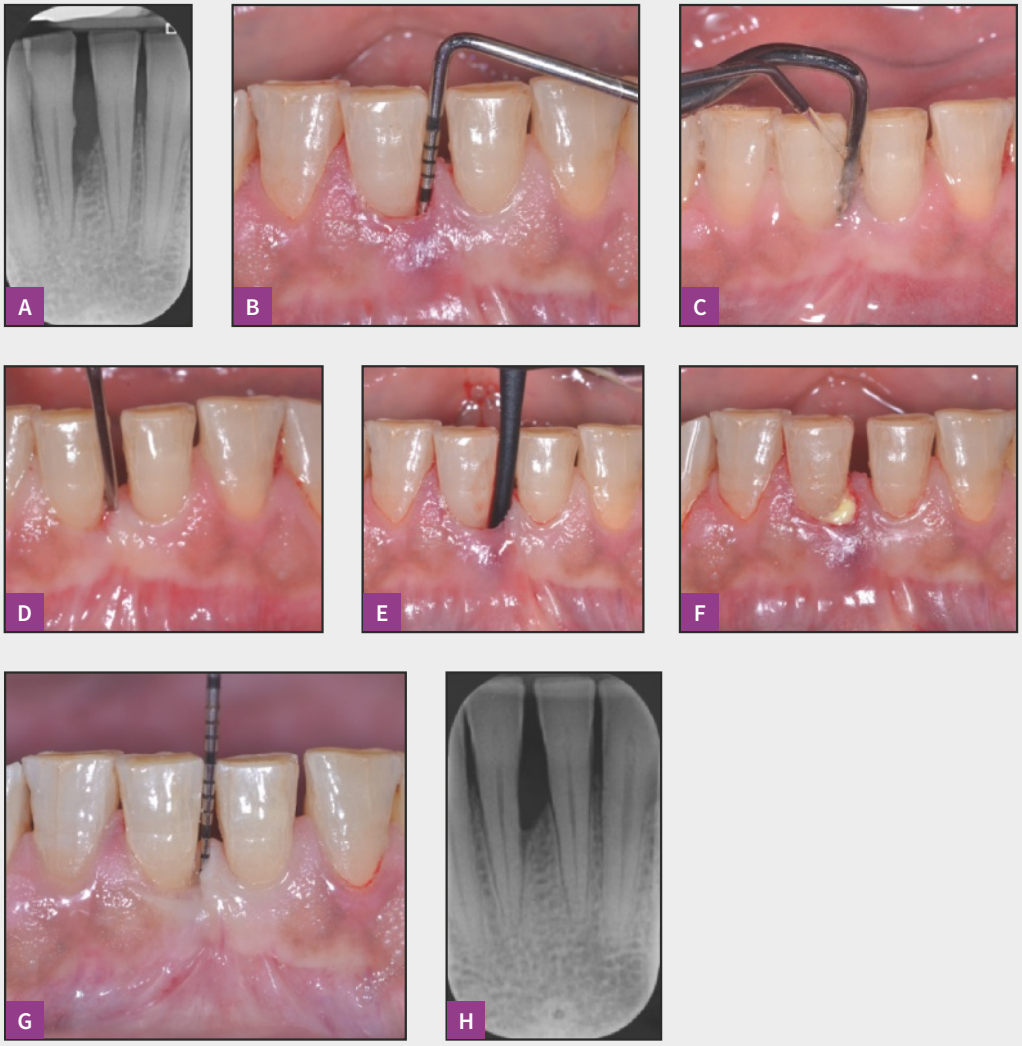


Fig 5 (A to F). *The non-surgical phase leads to the resolution of inflammation by removing etiologic factors by means of professional elimination of irritants, the delivery of proper oral hygiene instructions, and the modification of other associated risk factors such as a smoking habit.*

Case 1 (Fig 6 A to H). Non-surgical therapy can be improved by adjunctive antibiotics in selected clinical situations. After conventional hand and ultrasonic instrumentation, slowly delivered 14% doxycycline hyclate gel (Ligosan, Kulzer) was locally applied with an optimal clinical resolution of the initial pocket and partial remineralization of the initial radiographic defect. (Courtesy of Marta Zambelli, Turin, Italy.)



Lessons learned from non-surgical management of periodontitis

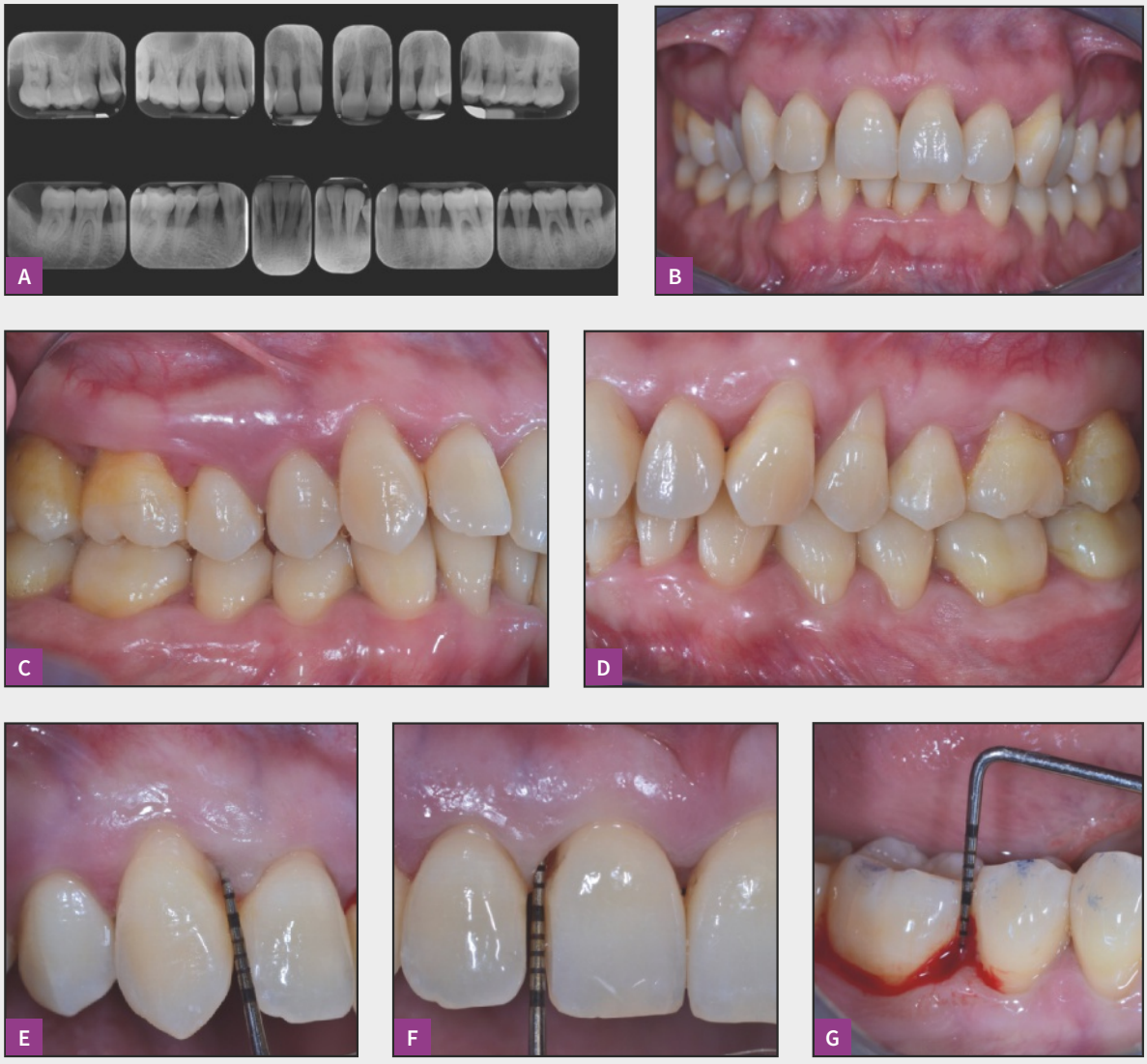
- Non-surgical therapy is effective in reducing PD and inflammation.
- Non-surgical therapy must precede the corrective surgical phase.
- Non-surgical therapy is often insufficient in completely resolving the disease.
- Efficient plaque removal is challenging, particularly in deep pockets.
- Oral hygiene measures are critical to sustaining long-term outcomes.
- Adjuvants such as the use of systemic antibiotics offer limited benefits.

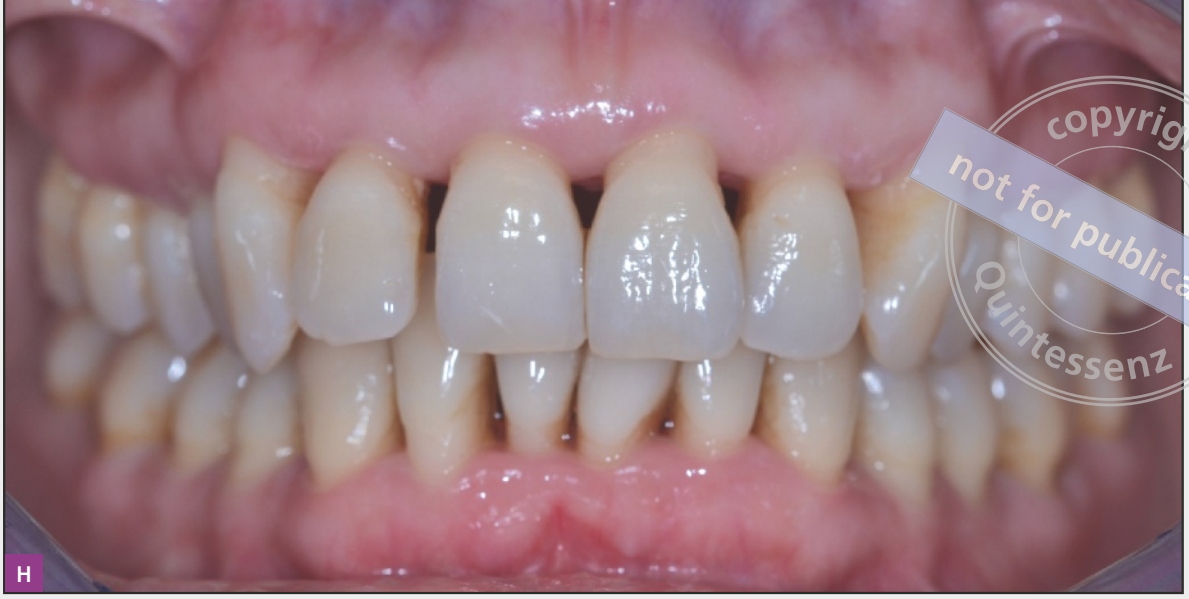
Reevaluation

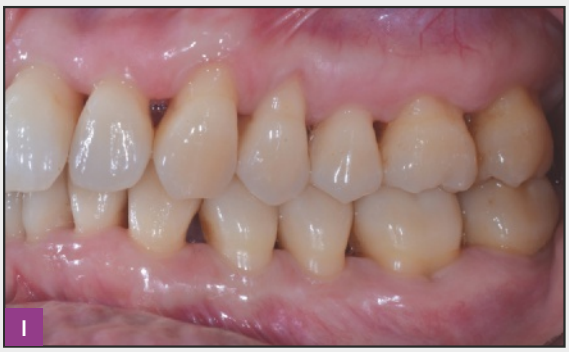
Clinical reevaluation must be performed ≥6 weeks after initial therapy. This is based on the pioneering preclinical findings demonstrated at the University of Michigan in a gingivectomy model. It was shown that epithelial cells migrate between the polyband (band of polymorphonuclear cells) and connective tissue 12 to 24 hours after surgery, reaching tooth structures in 5 to 7 days. It was further demonstrated that functional arrangement and collagenous maturation of connective tissue requires up to 5 weeks. Hence, it seems reasonable to wait ≥6 weeks to guarantee the maturation of the connective tissue and minimize the odds for overestimation of disease severity.[20,21]

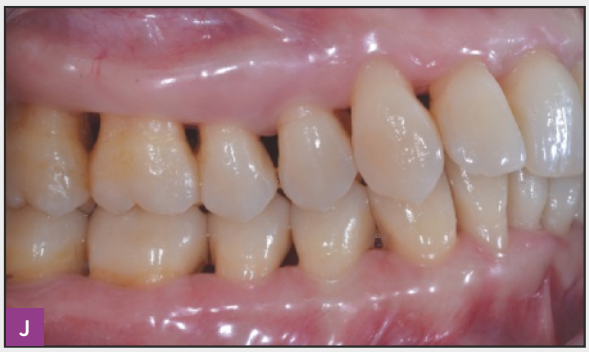
Reevaluation is required to optimize efficiency in terms of disease control. Clinical changes need to be recorded and compared to baseline. This will aid in decisions regarding future steps needed to achieve stability. If the reevaluation shows periodontal and peri-implant health and there is no deformity that compromises esthetics or long-term health, the patient can be placed on a supportive periodontal/peri-implant maintenance therapy schedule (for more details see chapter 10). If, on the contrary, long-term stability cannot be guaranteed or residual PD ≥6 mm is still present together with inflammation, corrective surgery might be indicated. It must be noted that compromised periodontal patients are more successfully managed with non-surgical therapy compared with patients with peri-implantitis, in whom results are less consistent.

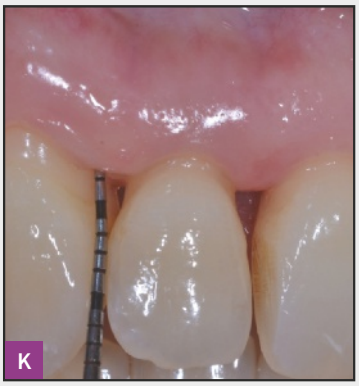
Case 2 (Fig 7 A to M). The non-surgical phase of treatment improves inflammatory conditions. Note that at reevaluation PD is significantly reduced although mostly due to post-instrumentation recession of the marginal soft tissues. (Courtesy of Marta Zambelli, Turin, Italy.)

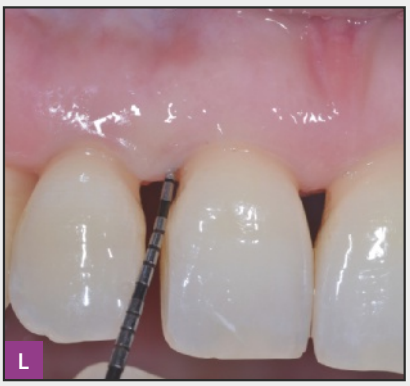


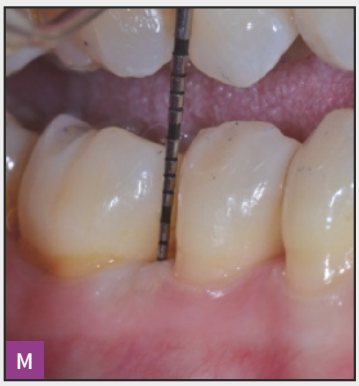












Lessons learned from reevaluation phase in the management of periodontitis

- Clinical reevaluation must be performed ≥6 weeks after initial therapy.
- Clinical changes have to be noted and compared to baseline.
- Reevaluation is the stage to decide further steps based on findings.
- Further steps must be considered if full-mouth plaque index and full-mouth bleeding index scores are <15% to 20%.

Phase II: Corrective phase

Rationale and indications

The primary goal in the surgical phase of periodontal and peri-implant treatment is to obtain access that will allow the clinician to see the etiologic factor(s). This enables more efficient maneuvers to remove irritants from the cementum/implant surface and periodontal/peri-implant tissue.

The corrective phase is indicated when disease resolution is not achieved by means of non-surgical therapy. This phase is also indicated in those cases in which, based on the existing features, the odds for disease recurrence are high. The corrective phase may further address esthetic defects or compromised oral function via prosthodontic and/or implant therapy.

The rationale for surgical therapy lies in the fact that deep pockets are more prone to association with pathogenic microflora capable of penetrating the tissues.[22] This may lead to recurrence and perpetuation of chronic inflammation. Long-term data indicated that residual PD ≥6 mm and BOP ≥30% after initial therapy may represent indications of disease progression.[23] In fact, these residual sites are often associated with more putative bacteria such as *Porphyromonas gingivalis*, *Prevotella intermedia*, or *Aggregatibacter actinomycetemcomitans*.[24]

In addition, it must be highlighted that the surgical phase plays a critical role in effective plaque removal. Ex vivo studies showed that complete calculus removal with non-surgical therapy in PD ≥4 mm is unpredictable; in fact, the maximum instrumentation is approximately 6 mm.[8] Hence, it seems reasonable that given the role of plaque removal on soft and hard tissue repair and fibroblast attachment on the cementum, surgical access is indicated. It should be emphasized that this is even more challenging at implant sites, in particular for those implants supporting fixed prosthesis with convex emergence profiles.

Significance and effectiveness in the management of periodontitis

In general terms, surgical therapy has shown effectiveness in moderate to severe pocket depths. The effectiveness proved to be linked to site-specific features and deleterious habits, including the presence of an exposed furcation, mobility, or a smoking habit[25,26]; however, in general, the response is very favorable for deep pockets. Longitudinal studies comparing various surgical and non-surgical therapeutic modalities demonstrated that pocket reduction/elimination procedures predictably result in probing pocket depth reduction, reduction in inflammation, and CAL gain.[13,27–30] It must be further noted that, no matter the type of surgical procedure, healing results in mucosal recession that may compromise esthetics.

Given that disease resolution is dictated by the elimination of inflammation and the reduction of probing depth, soft tissue must be supported by a level bone topography (Fig 8). It therefore is suggested to tailor the surgical modality to achieve a flat or positive architecture. In this context, three different case scenarios can be presented:

1. Contained defects (infraosseous defects)
2. Uncontained defects (supracrestal defects)
3. Combined defects (combination of infraosseous and supracrestal defects)

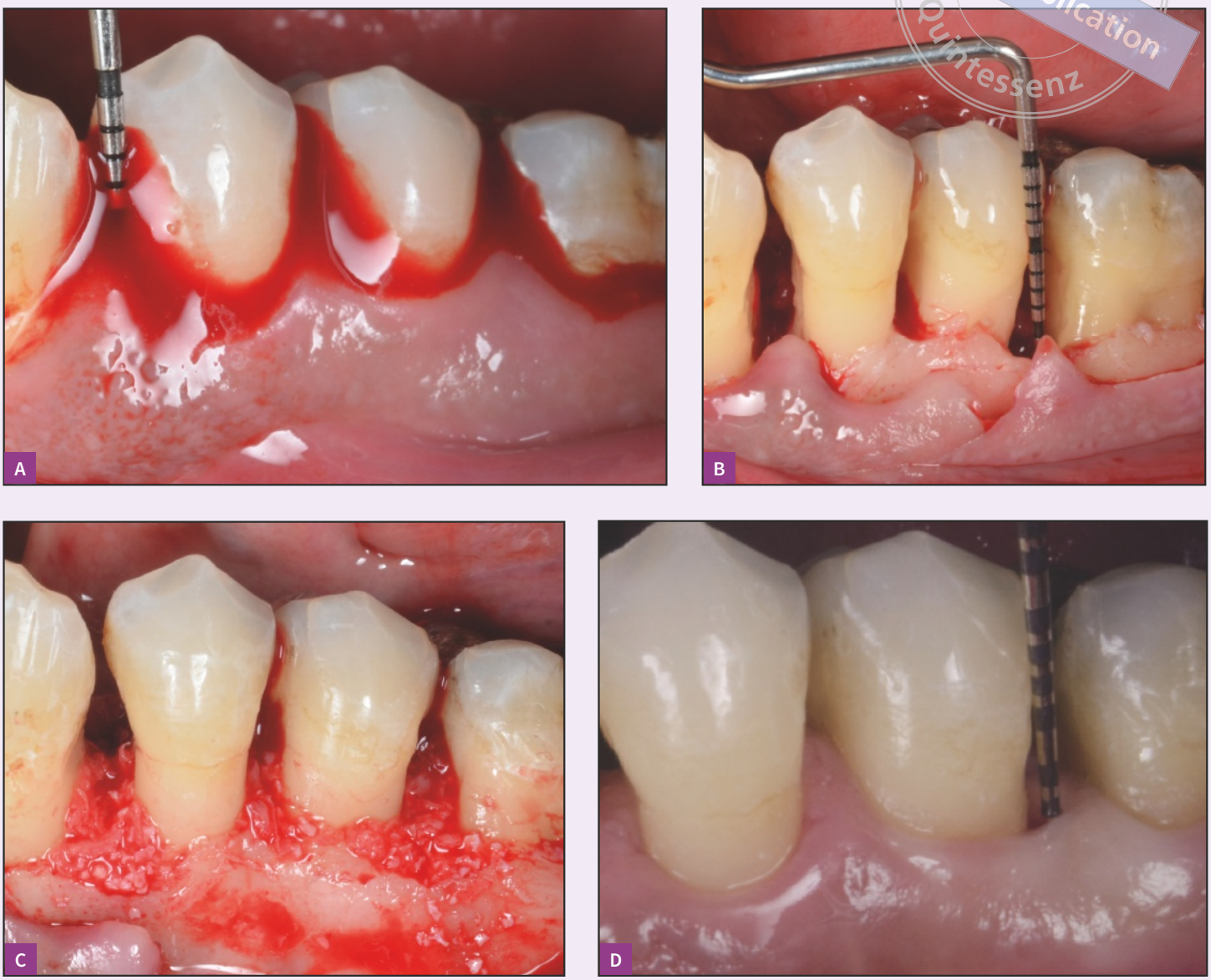
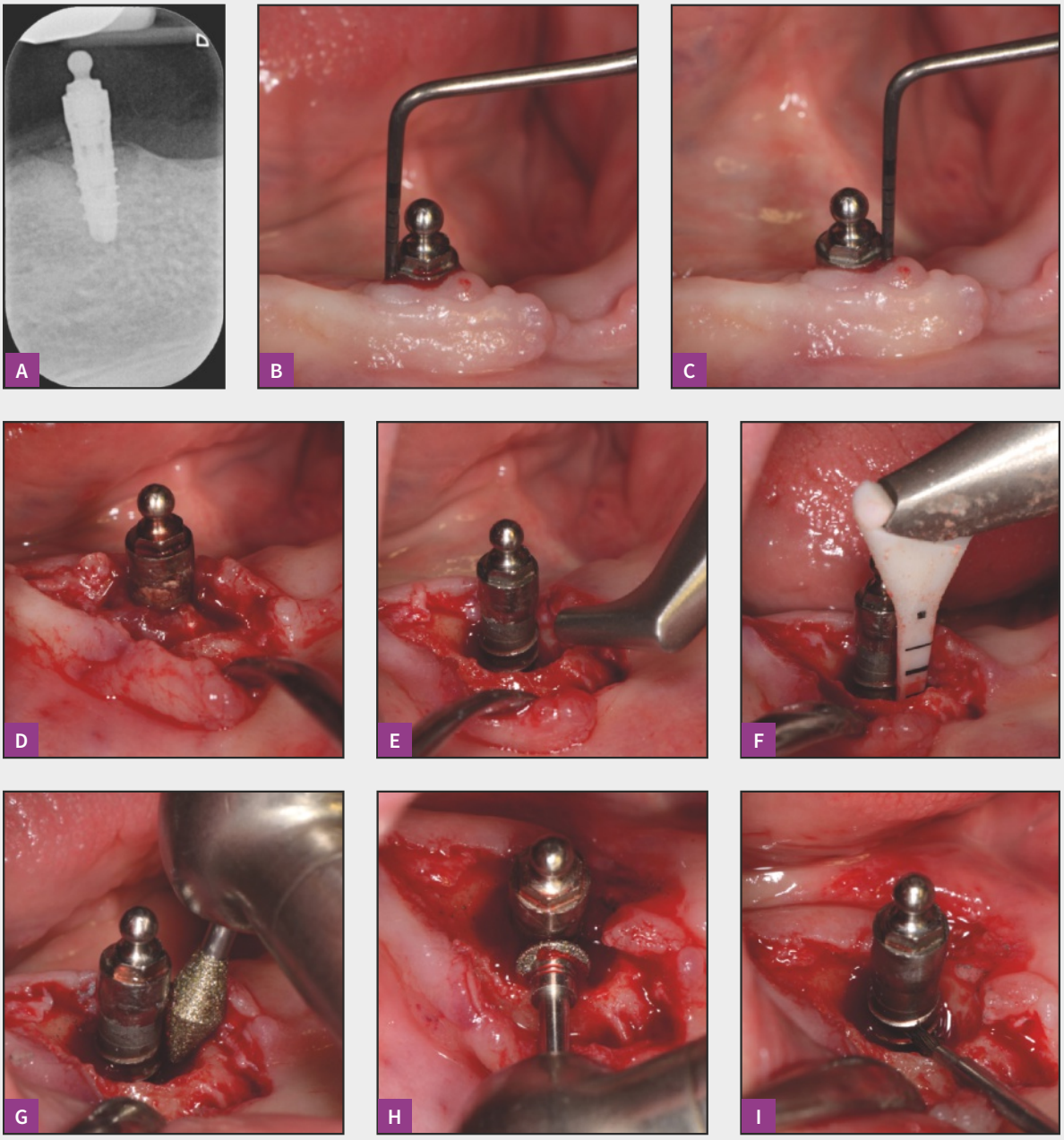
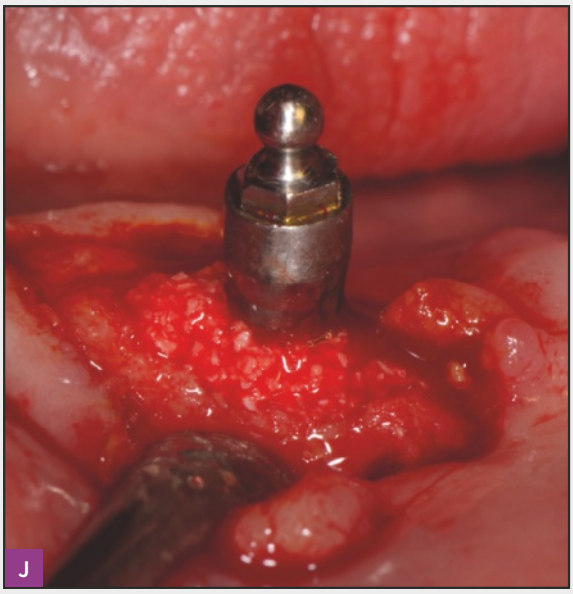
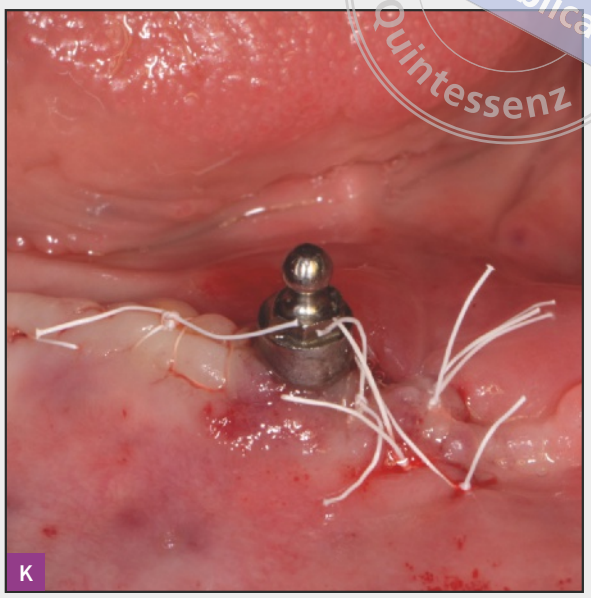


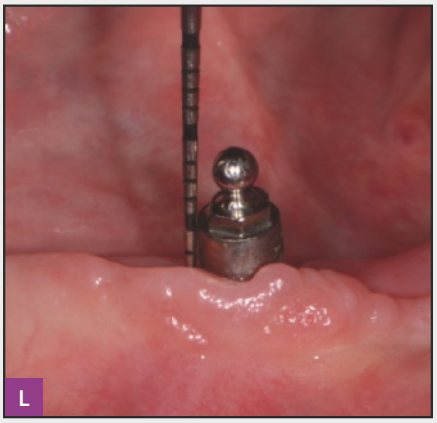
Fig 8 (A to D). *The surgical therapeutic modality indicated in the management of periodontitis is guided by the defect configuration and defect depth, with the goal of achieving a flat or positive architecture. Note disease resolution and substantial PD reduction at 24-month follow-up.*

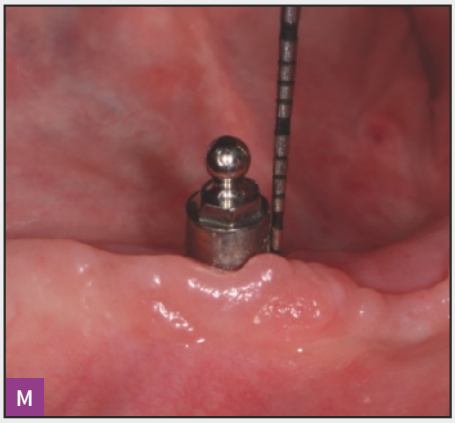
Case 3 (Fig 9 A to N). The surgical therapeutic modality of peri-implantitis follows the same criteria of periodontitis. When treating a combined peri-implant defect, in the supracrestal component soft tissue height will be reduced, and implant macro-geometry will be polished, with thread removal by means of diamond and rubber burs (Peri-Set, Sweden & Martina); in the intrabony component granulation tissue will be removed by means of air polishing with erythritol powder (Air-Flow Plus, EMS), and the implant surface will be debrided and polished by means of titanium brushes (Peri-Set). Only the intrabony component will be regenerated with anorganic bovine bone mineral (Bio-Oss, Geistlich) and fibrin sealant (Tisseel, Baxter). With this selective technique, PD can be significantly reduced and the bone defect filled. Note the disease resolution at the 1-year follow-up.

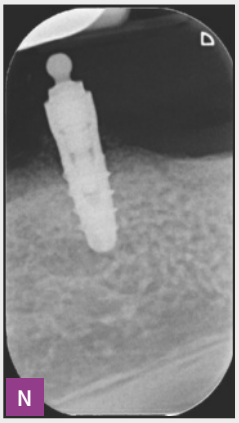




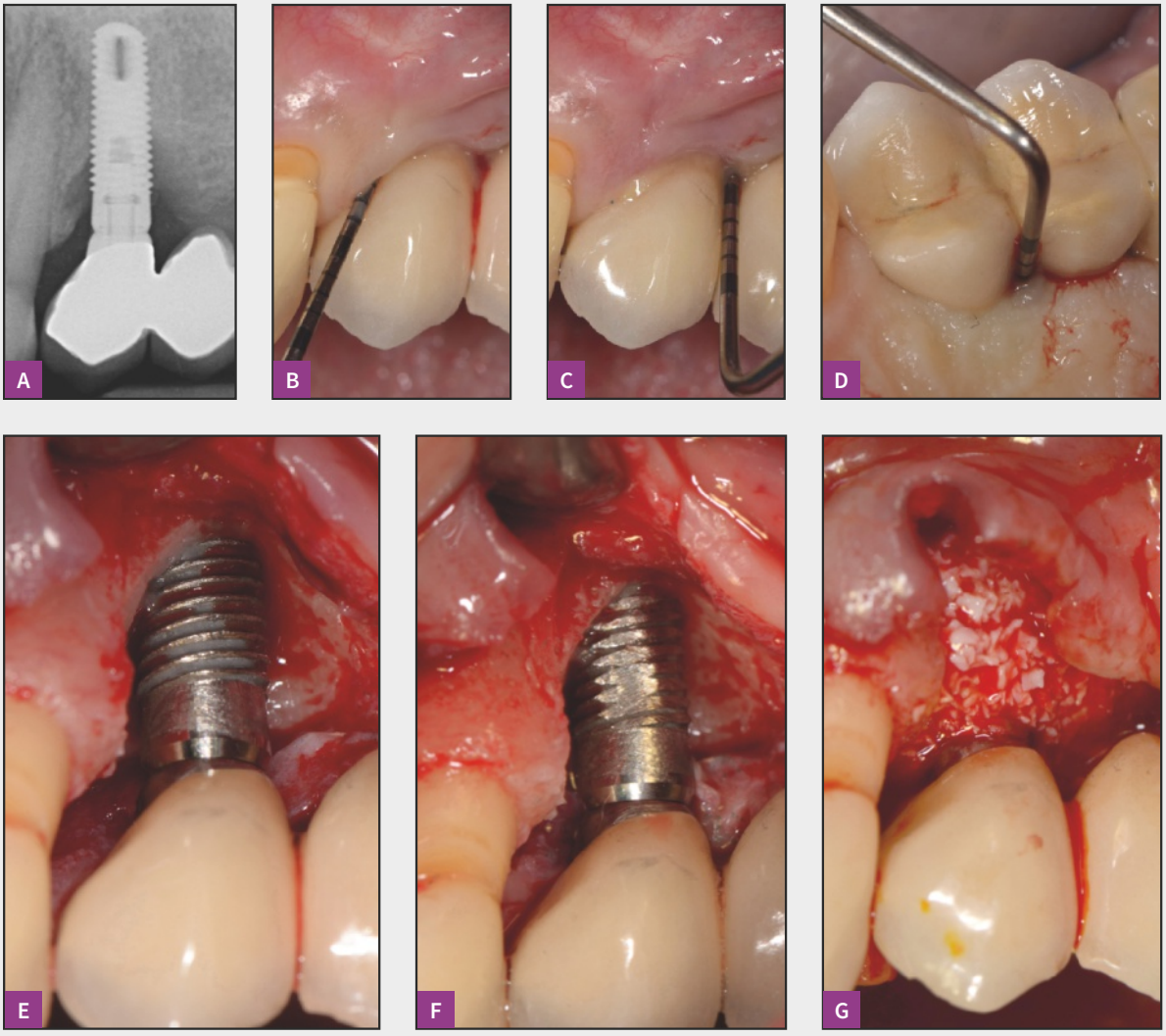


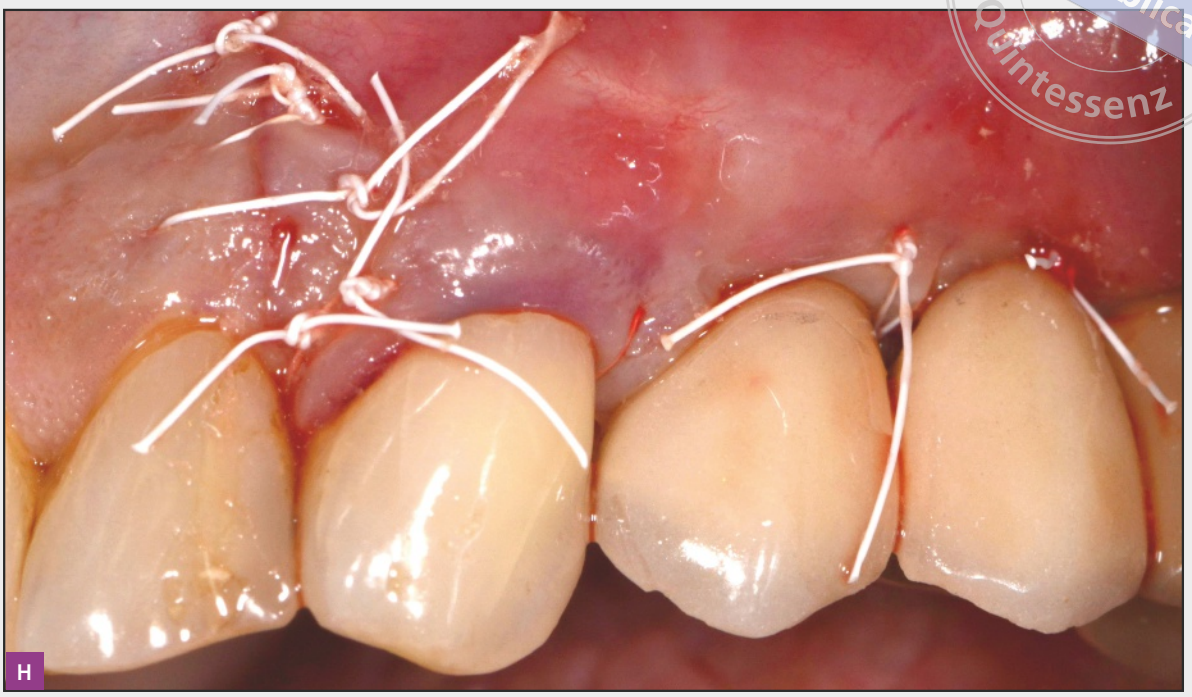




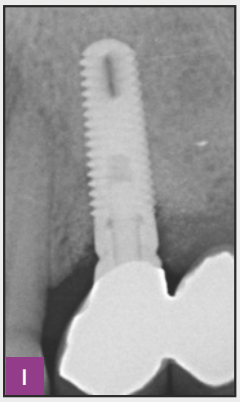


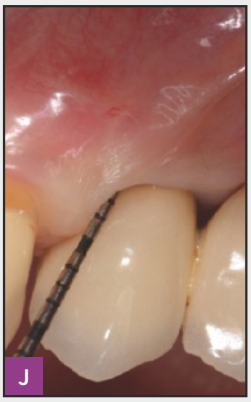
Case 4 (Fig 10 A to P). The selective approach to the instrumentation of the implant surface has been applied in this peri-implantitis case. By eliminating implant threads on the buccal side, the entire implant profile has been kept inside the horizontal bony envelope, thus creating a more favorable defect to be regenerated with anorganic bovine bone mineral (Bio-Oss) and fibrin sealant (Tisseel). Note the soft and hard tissue stability at 1- and 5-year follow-up.

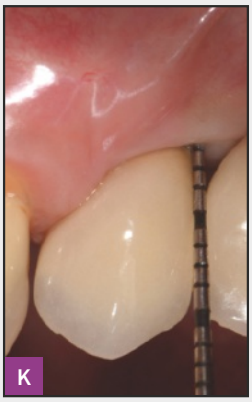


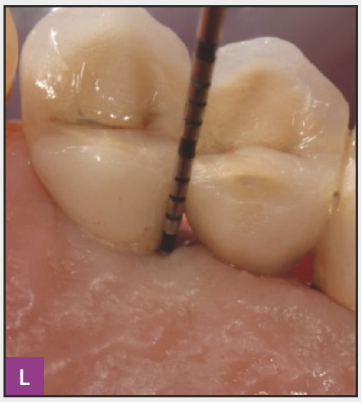


1 year follow-up

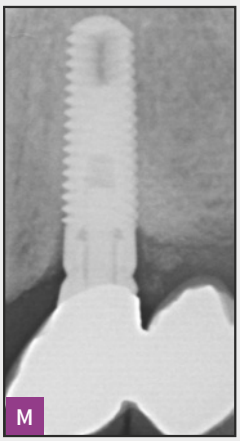


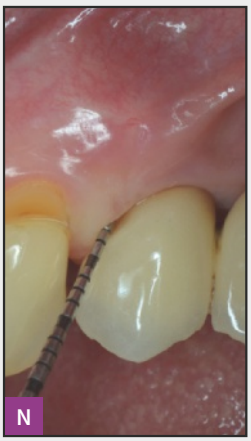


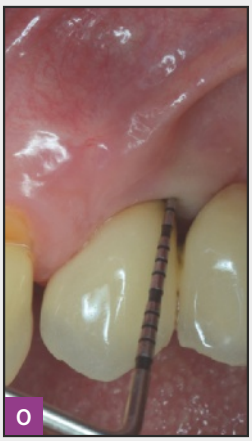


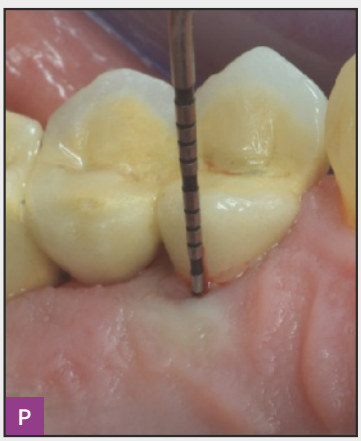


5 year follow-up

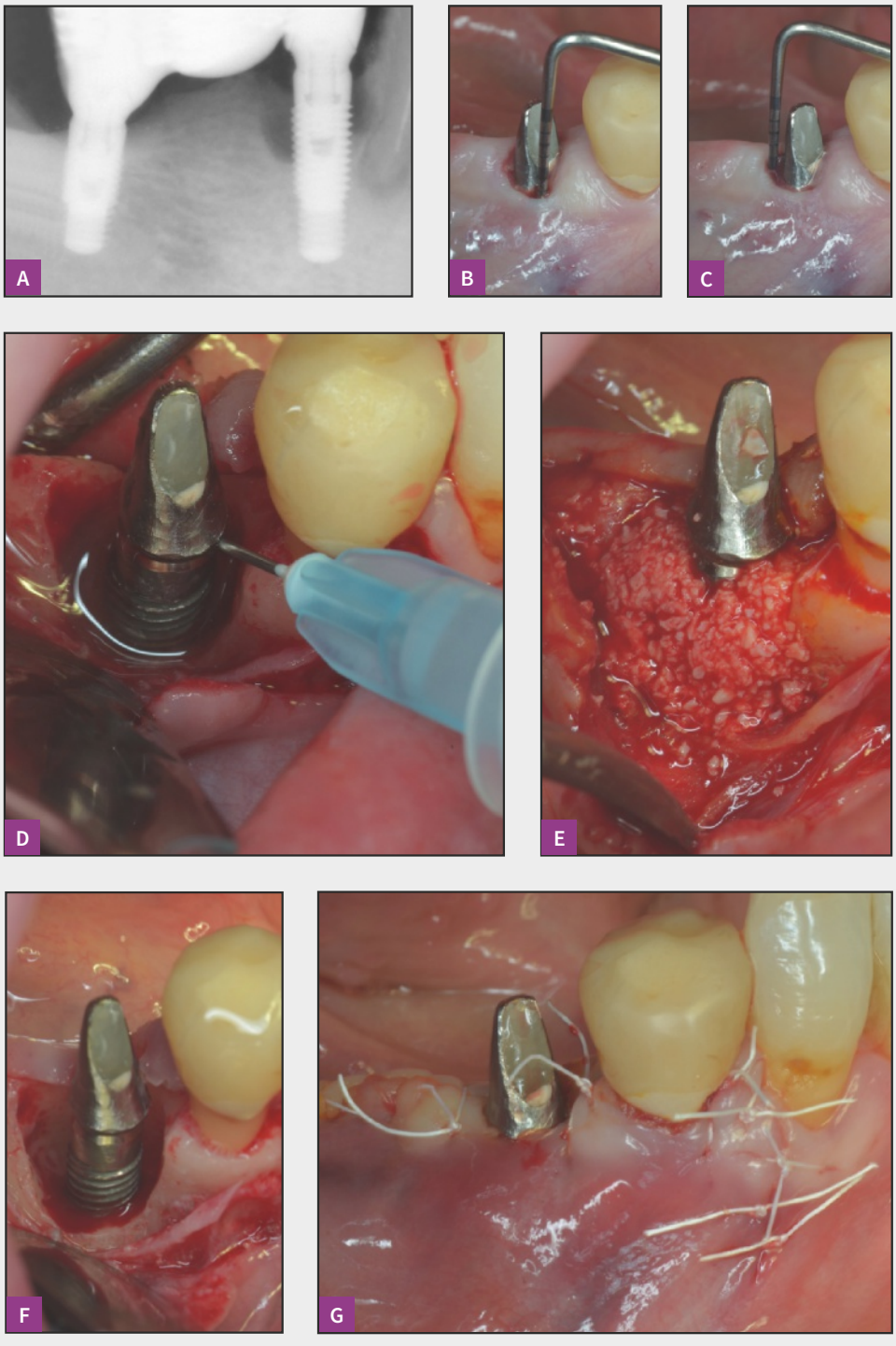


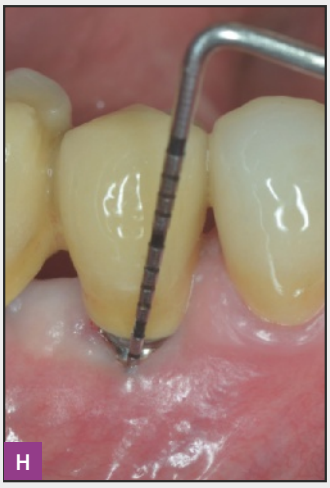


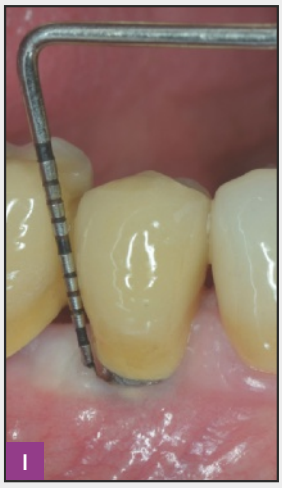


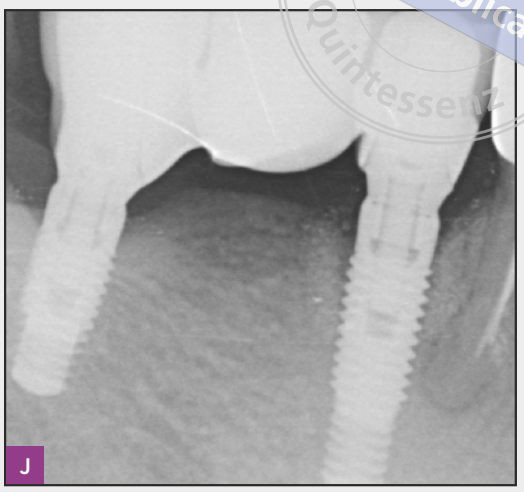


Case 5 (Fig 11 A to J). Implant instrumentation by means of titanium brushes, in this case improved with chemical decontamination of the surface (PeriSolv, RLS Global), has been used in the treatment of this completely infraosseous defect due to peri-implantitis. Anorganic bovine bone mineral (Bio-Oss) and fibrin sealant (Tisseel) were used in association with a volume-stable collagen matrix (Fibro-Gide, Geistlich) to improve the condition of the initially very thin buccal soft tissue, and both PD reduction and elimination of BOP has been achieved. Note soft and hard tissue stability at 1-year follow-up.









Defect configuration and depth are key factors in assessing the plausibility of a therapeutic modality. While, in general terms, it has been advocated to reconstruct lost or injured periodontal and peri-implant tissues using the principles of guided tissue/bone regeneration, the effectiveness in uncontained defects is generally null. As such, numerous classifications, clinical guidelines, and techniques were described within the field of periodontology to manage periodontal lesions.[31–33] Lessons learned from findings within the field of periodontology, including indications and effectiveness, can be found below according to the therapeutic modality (Table 2).

Lessons learned from the surgical phase in the management of periodontitis

- The corrective surgical phase is often needed to access and remove the etiologic factor in cases of moderate to deep PD.
- Access surgical therapy is effective in PD reduction and CAL gain.
- Surgical therapy results in gingival/mucosal recession.
- The surgical modality has to be tailored to the clinical and radiographic scenario.
- The purpose of the surgery dictates flap design.
- Defect configuration and depth are key to understanding the feasibility and effectiveness of the surgical therapeutic modality.

Bone regeneration in the management of periodontitis

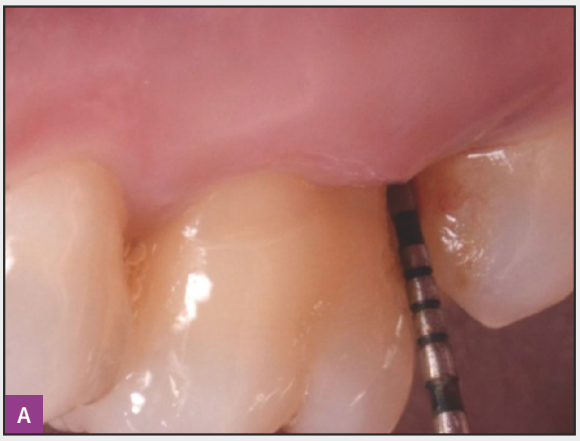
Rationale and indications

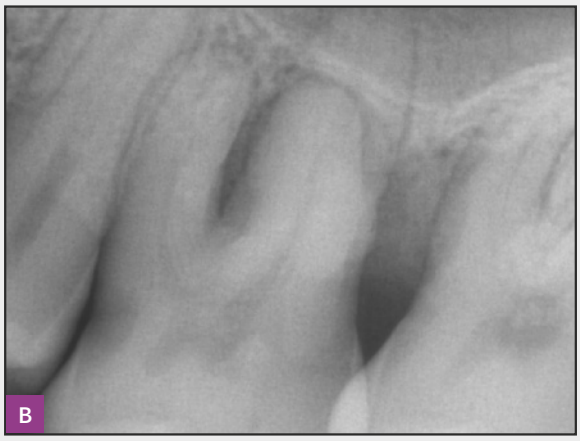
Bone regeneration at periodontitis and peri-implant sites is based on the principle of "compartmentalization" proposed in the 1970s.[34] In summary, it called for the creation of different compartments via a barrier membrane to exclude undesired soft tissue cellular ingrowth. Several technical modifications have been proposed to minimize trauma and enhance the therapeutic outcome.[35–37] In fact, in the last decades biomaterials have been significantly enhanced in terms of physical and biologic properties to make bone substitutes and barrier membranes easier to manage and more effective in promoting early healing.

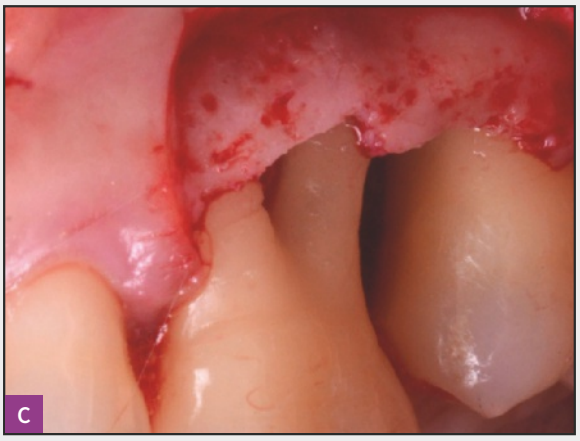
The following therapeutic goals are desired when applying the principles of guided bone regeneration:

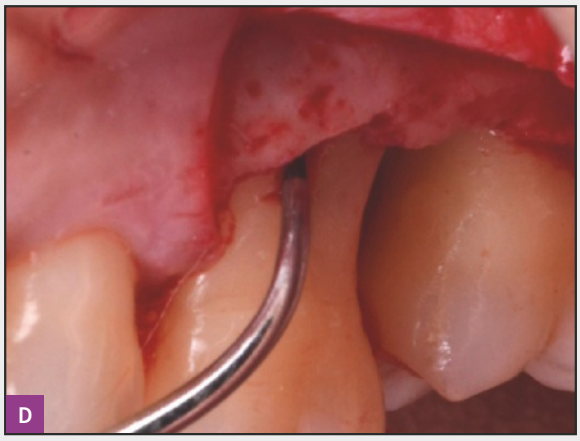
- PD reduction/elimination
- Restoration of the alveolar process
- Regeneration of the functional attachment apparatus at teeth
- Re-osseointegration at implants

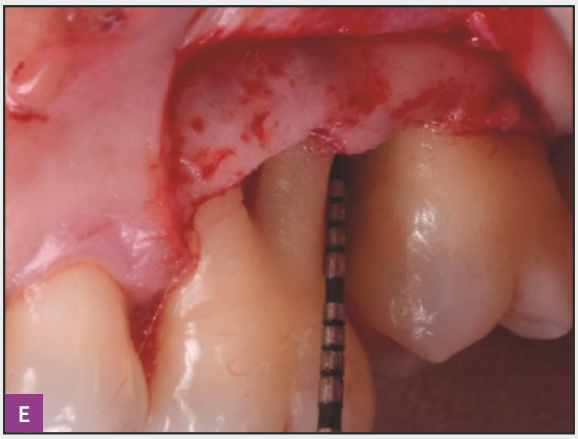
Case 6 (Fig 12 A to J). Advanced interproximal attachment loss and furcation degree III in a patient diagnosed in a Stage IV, grade B of periodontitis. After comprehensive debridement and root scaling mineralized cortical allograft (Lifenet) is used to graft the intrabony component. A moldeable demineralized graft (ORAGRAFT Prime, LifeNet) is adapted to the defect to provide further stability to the particled graft and supply osteoinductive potential. Reevaluation at 6-month follow-up indicates resolution of inflammation, pockets depth compatible with health (4mm) and significant radiographic bone fill. Patient is under strict supportive periodontal maintenance therapy.

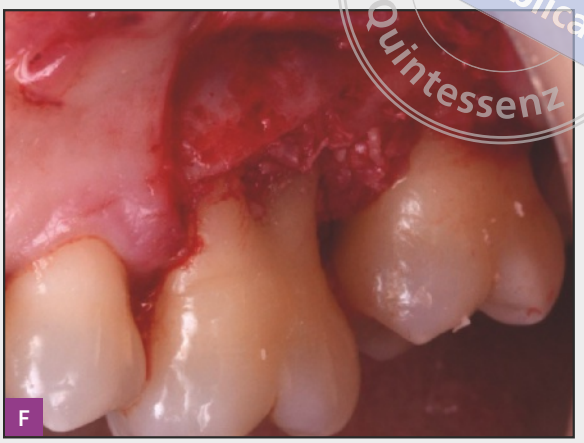


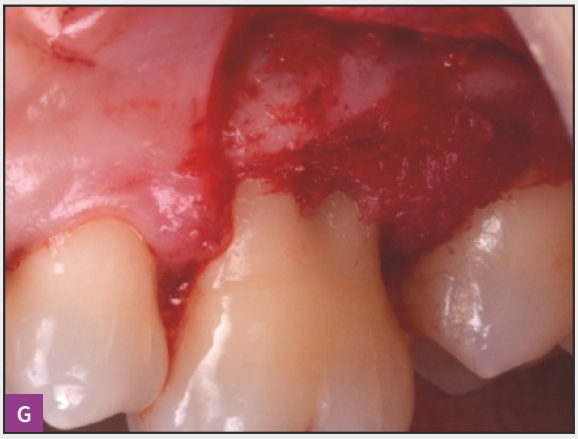


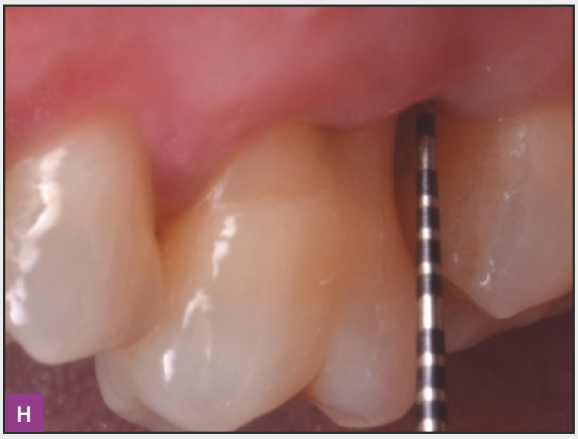


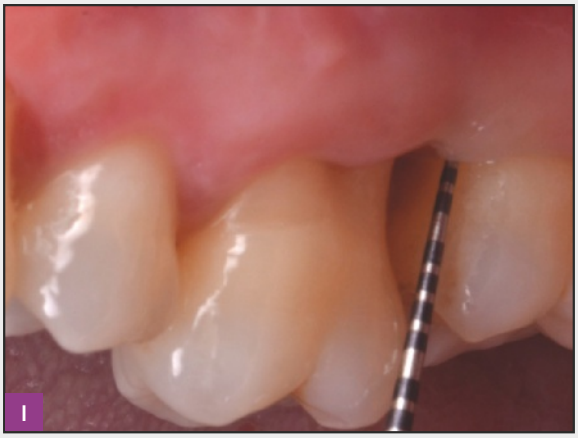


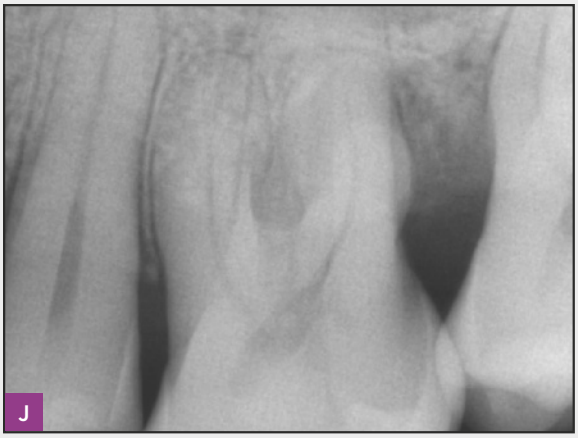












As mentioned previously, bone regeneration procedures are indicated for contained defects, defined as 3- or 4-wall, narrow, deep defects. Therefore, shallow and wide 1- or 2-wall defects are not prone to favorable outcomes when regenerating.[38] Evidence demonstrated that the bone defect angle is significant when assessing the therapeutic prognosis. As such, periodontal defects narrower than 45 degrees tend to repair in an efficient manner.[39] This understanding has been further demonstrated at peri-implantitis sites.[40]

The biological[41] and technical[42,43] principles advocated for in guided tissue/bone regeneration/repair are presented in Table 2.

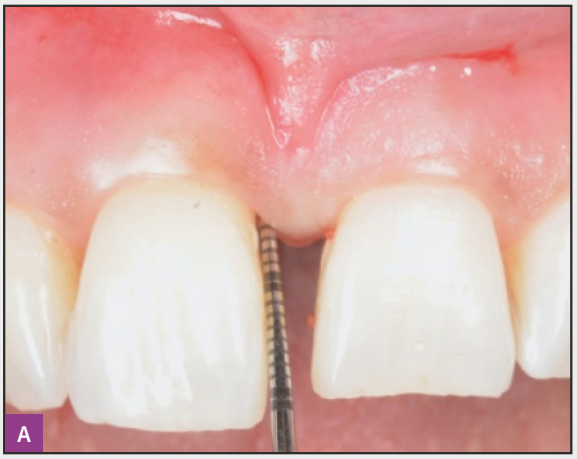
Table 2. *Principles for successful guided tissue/bone regeneration*

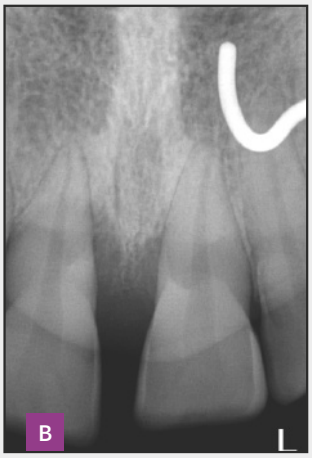
Principle	Purpose	Intervention
Primary wound closure	Undisturbed healing by means of tension-free flap closure	Incision design
Angiogenesis	Supply of oxygen and nutrients	Decortication
Space creation	Supply space and prevent collapse	Membrane and bone filler selection
Stability of the blood clot	Blood clot formation	Wound closure

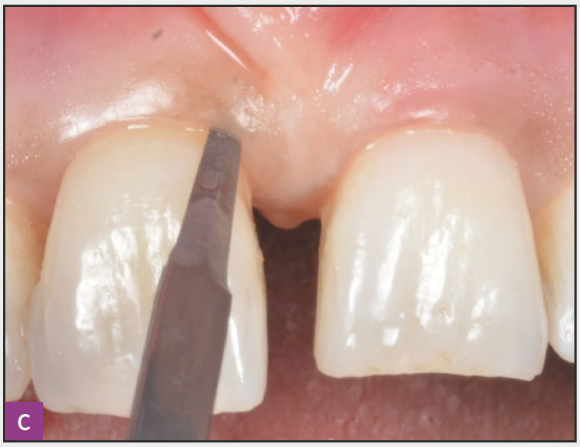
Significance and effectiveness in the management of periodontitis

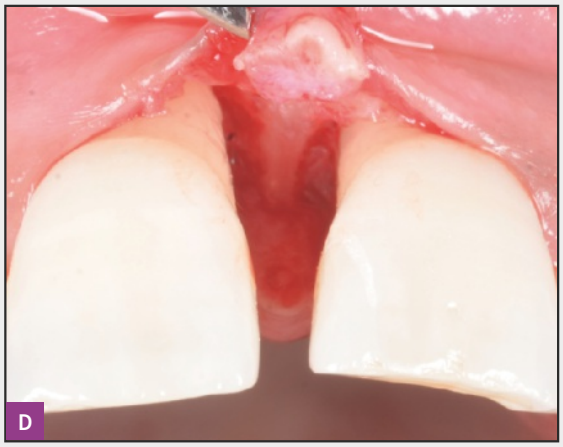
Tissue regeneration has been widely investigated since the proof of concept was described.[44,45] Since then myriad clinical and preclinical studies have shown bone reconstructive procedures to be plausible and effective in gaining clinical attachment level and radiographic bone fill, reducing PD, reducing the level of inflammation, and arresting disease progression.[38,46–49] Nevertheless, this intervention does not prevent gingival/mucosal recession, which in turn may affect the esthetic outcome.[50,51]

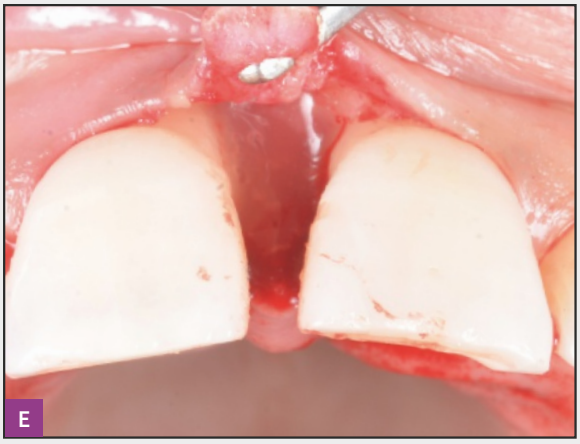
Case 7 (Fig 13 A to L). The potential of guided tissue regeneration assisted by the use of demineralized allogeneic bone particles (OraGraft, LifeNet Health), enamel matrix derivative (Emdogain, Straumann), and a porcine resorbable membrane (Creos Xenoprotect, Nobel Biocare) depends on the defect depth and configuration. Note the complete radiographic defect fill with residual PD of 3 mm and no bleeding or inflammation at the 36-month follow-up during orthodontic therapy.

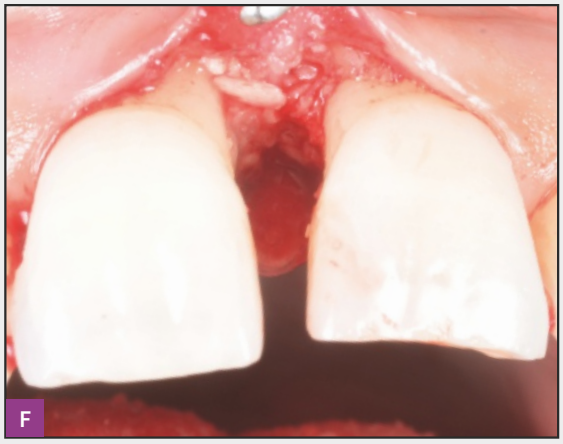


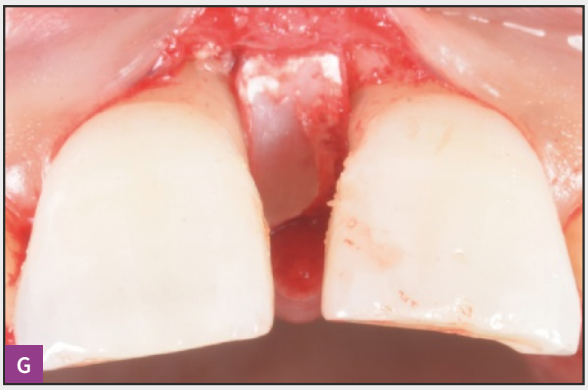


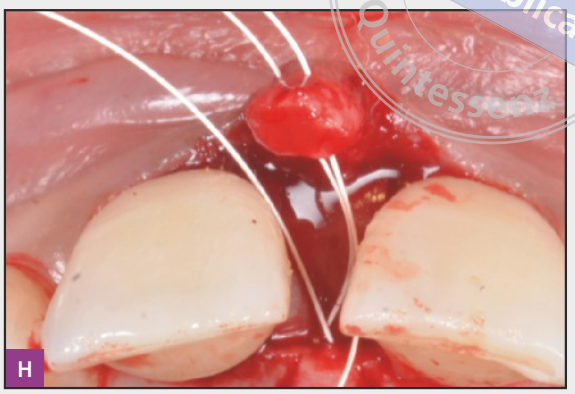


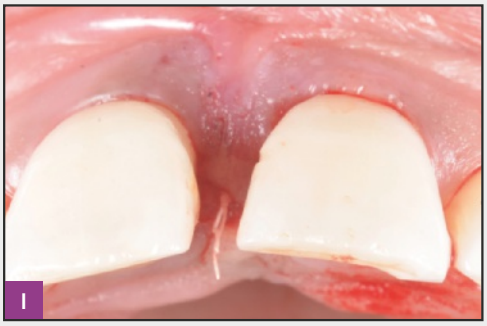


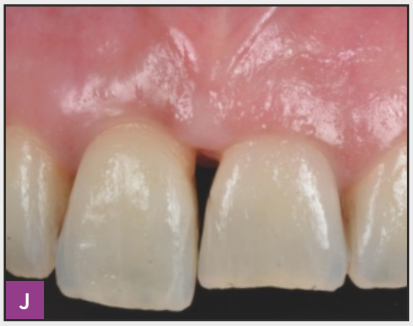


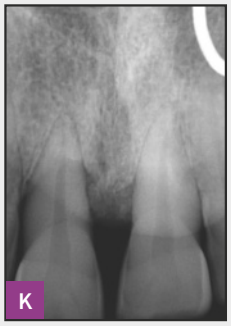


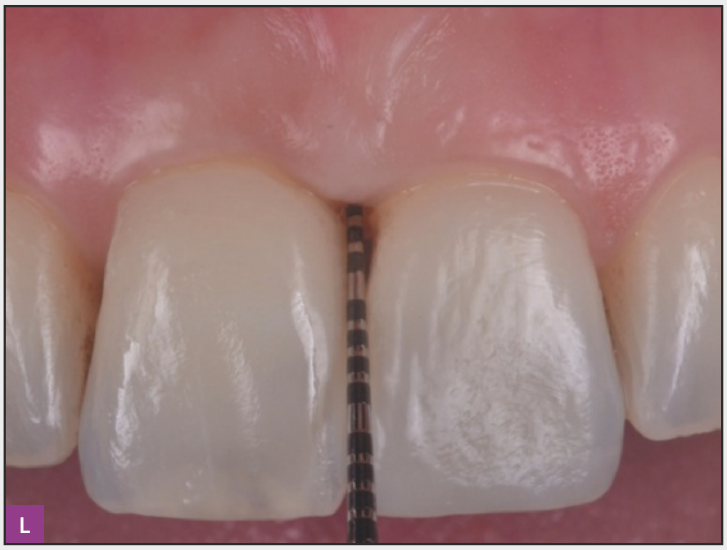






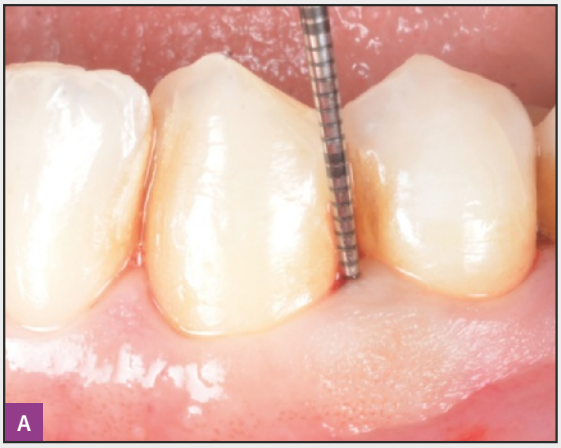


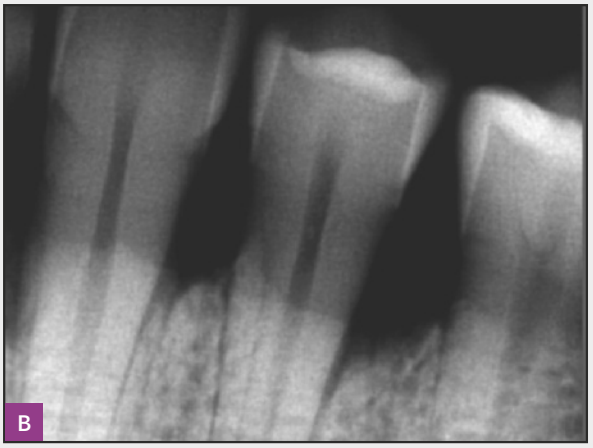


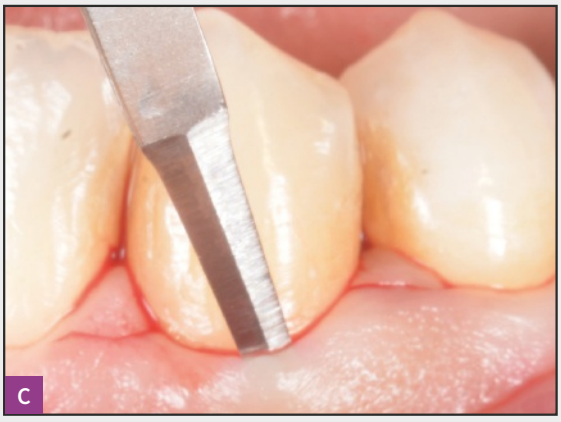


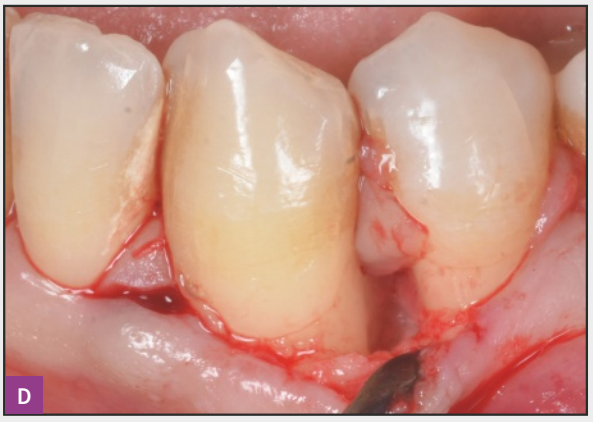
Tissue regeneration procedures have been shown to outperform access flap surgery in CAL gain by approximately 1.5 mm.[52] Furthermore, the effectiveness of fulfilling the principles of guided tissue/bone regeneration by means of applying barrier membranes for cell exclusion has been validated.[53] It seems that the addition of bone substitutes further improves the CAL when combined with resorbable membranes or enamel matrix derivatives.[52] Recent evidence has shown promising outcomes of platelet-rich aggregates in further optimizing the regenerative outcomes at sites with lost or injured periodontium.[54] Reconstructive therapy for the management of peri-implantitis has proved beneficial in terms of PD reduction of approximately 3 mm and radiographic bone gain of approximately 2 mm.[55] Based on the existing literature, however, reconstructive therapy has not shown evident benefits compared to open access surgery.[56]

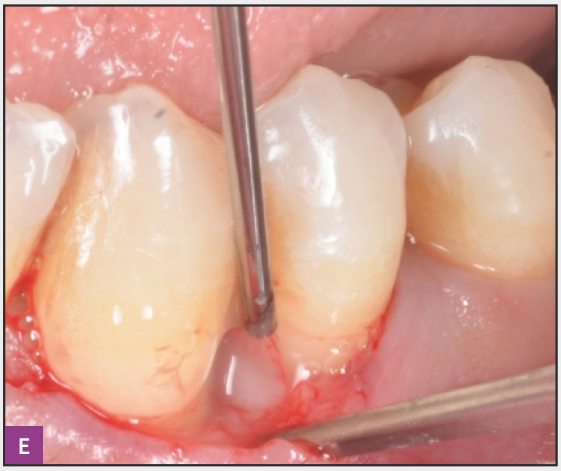
Case 8 (Fig 14 A to F). Minimally invasive regenerative procedures can be applied to minimize trauma and tissue collapse. In this case enamel matrix derivative (Emdogain) was used to promote soft and hard tissue healing. Note the clinical resolution at the 30-month follow-up.

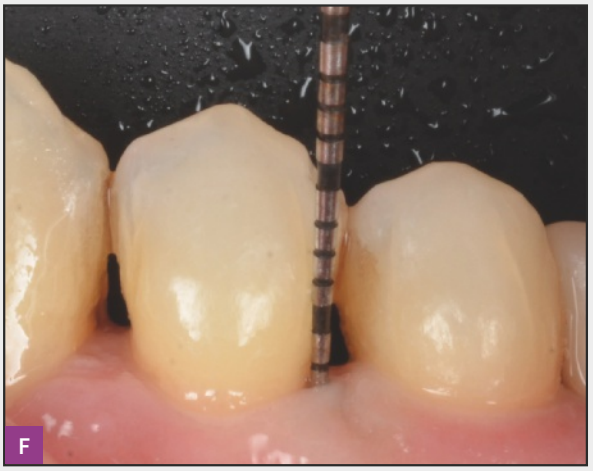




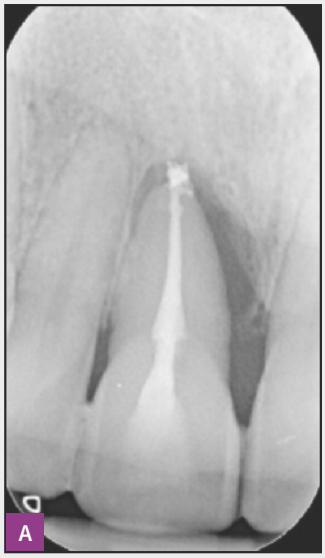


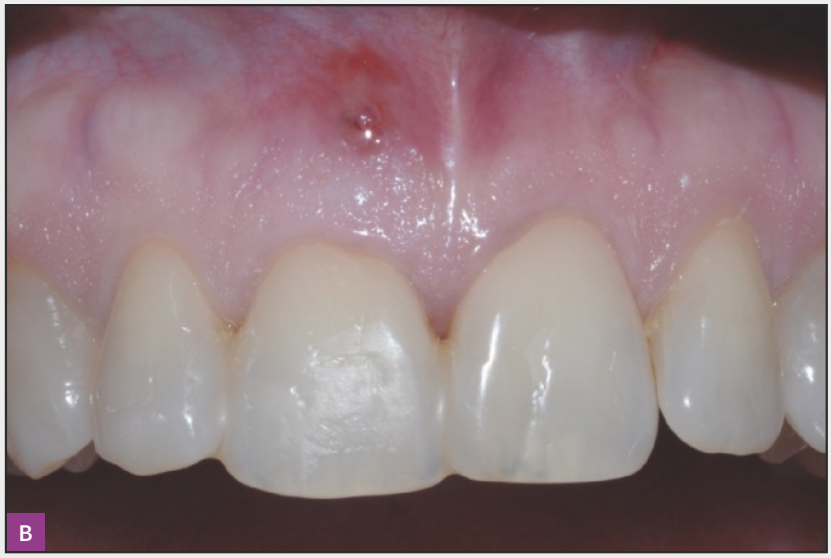


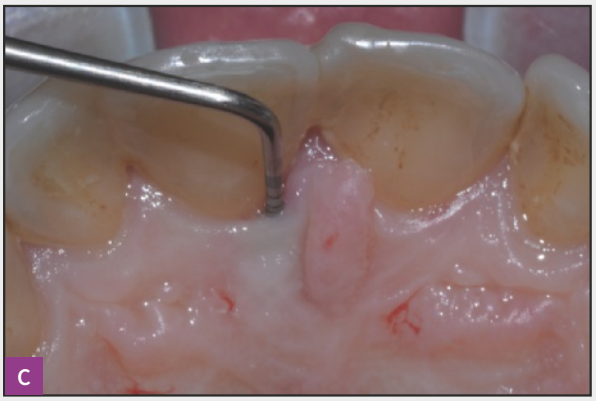


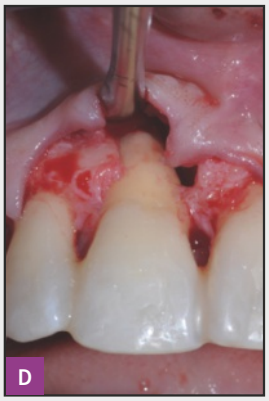


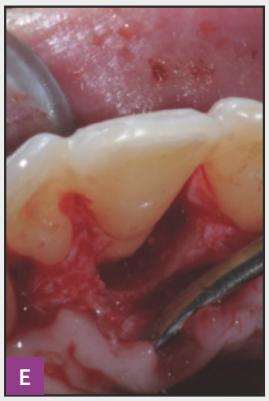
Case 9 (Fig 15 A to K). Guided tissue regeneration is very powerful, even in cases with intrabony defects reaching the apex or beyond. Anorganic bovine bone mineral (Bio-Oss) particles plus enamel matrix derived proteins (Emdogain) were used to fill the defect. Note the complete radiographic defect fill with a residual PD of 3 mm and no BOP at the 5-year follow-up visit.

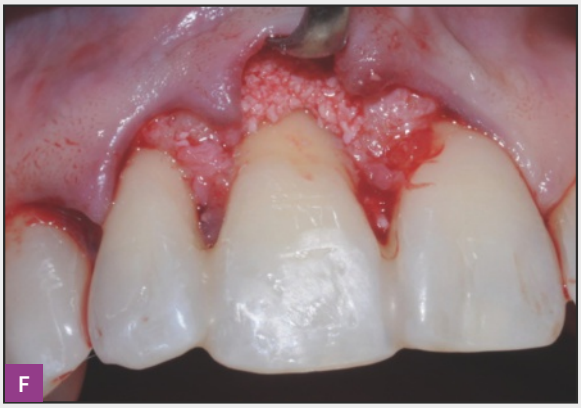


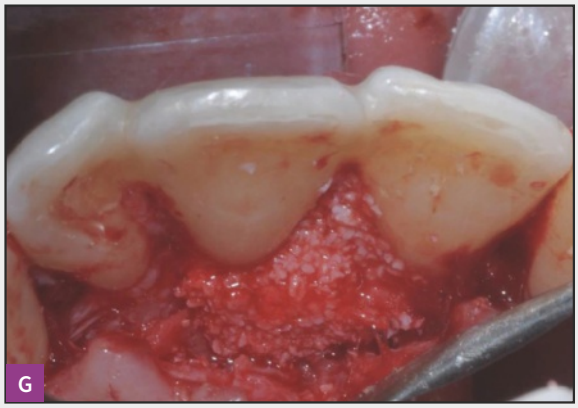


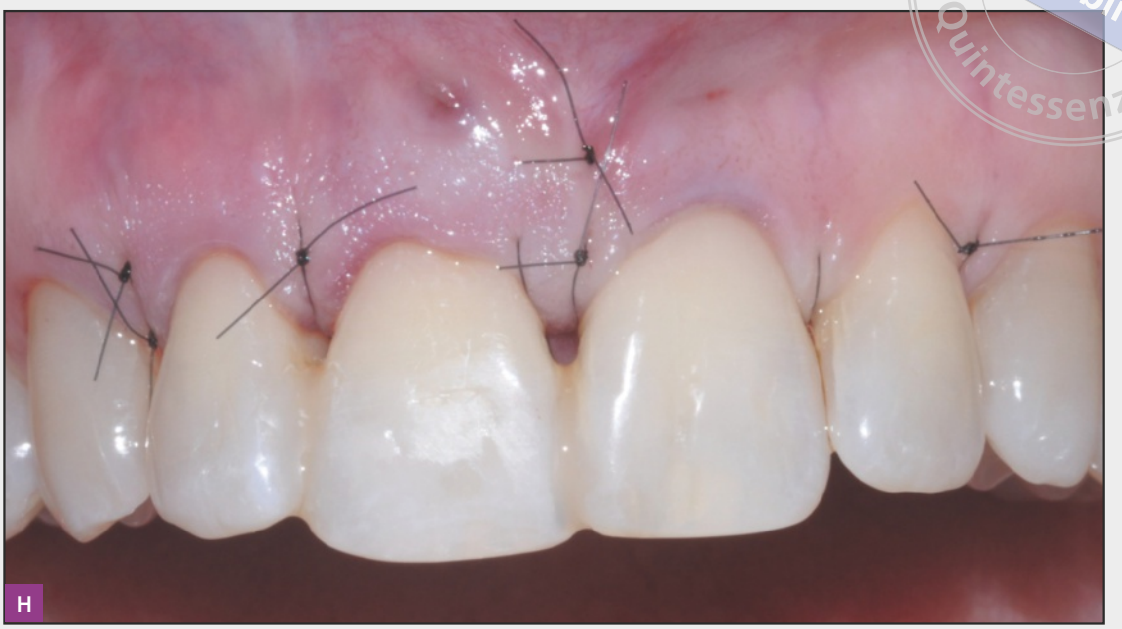








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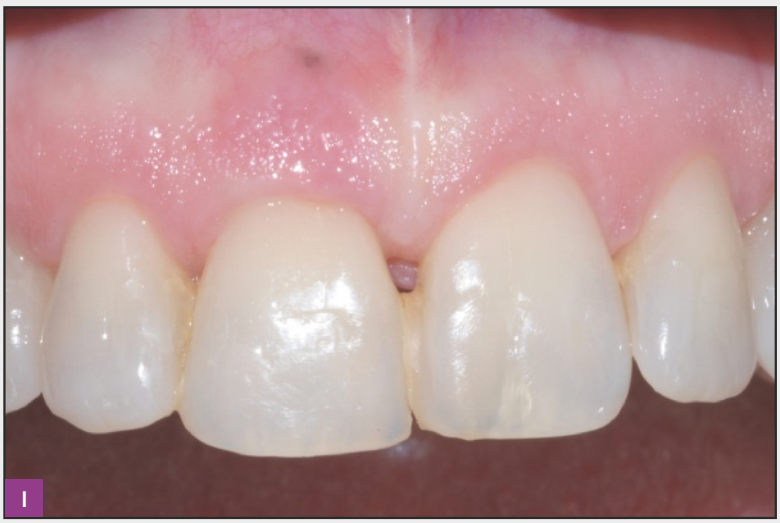
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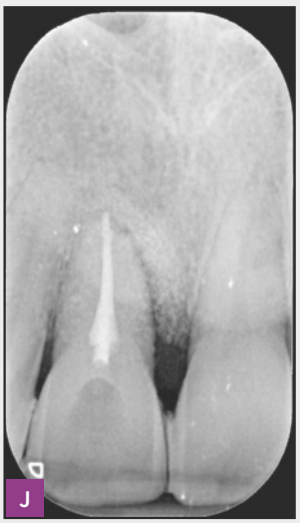
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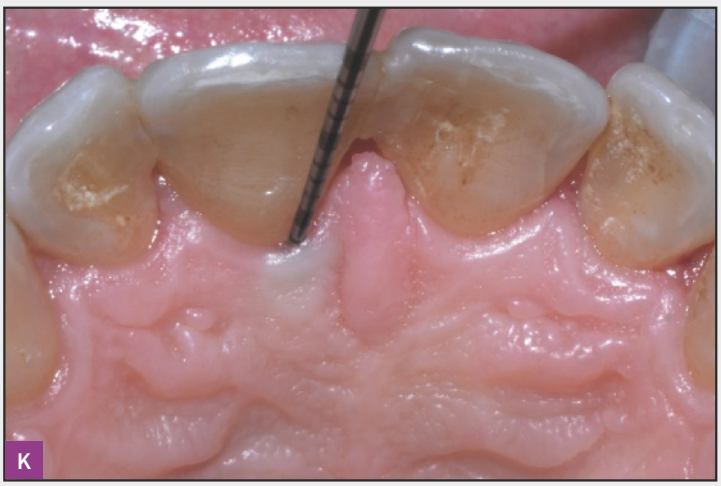
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Lessons learned from reconstructive therapy in the management of periodontitis

- The application of the concept of guided tissue regeneration has been shown to be plausible and effective in the management of periodontitis.
- Bone reconstruction at periodontitis sites is more efficient in narrow and contained defects.
- Hard tissue regeneration with or without membrane is effective in reducing PD and gaining CAL.
- Reconstructive therapy results in mucosal recession of about 1 to 2 mm.
- The use of biologic agents and growth factors is promising to optimize the therapeutic outcomes.

Resective surgery in the management of periodontitis

Rationale and indications

For supracrestal pockets where no containment is present, resective surgery is indicated. This therapeutic modality has to be tailored to the clinical scenario with the goal of reducing/eliminating periodontal pockets. This means that soft and hard tissue have to be harmoniously managed by means of gingivectomy (or gingivoplasty) and ostectomy (or osteoplasty) based on the therapeutic endpoint.

Hence, this modality is indicated in shallow 1- and 2-wall uncontained defects were the reparative potential for hard tissues is limited. Considering the unpredictable outcomes of regeneration procedures in smokers,[57] resective surgery should be considered in borderline situations in these patients. Moreover, this approach appears to be less sensitive to inadequate oral hygiene compared to regenerative procedures.[6] Hence, in high-risk individuals such as those with erratic compliance to maintenance therapy, resective surgery may provide more predictable outcomes.

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