The Peri-Implantitis: Implant Surfaces, Microstructure, and Physicochemical Aspects

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ABSTRACT

There are two ways of looking at secondary failures of osseointegration; one is to reflect on possible causes for the failure, the other focuses on the pathology per se. In the first case, background factors such as mechanical trauma (adverse loading) or inflammations/infections are being discussed as the cause of failure. Then peri-implantitis is a term reserved for implant disturbance due to inflammation/infections only. However, irrespective of the original reason for the failure being adverse loading or inflammation/infection, the end result with bone resorption and inflammation may be very similar. Hence, in the present article, an alternative outlook has been chosen. Trigerring factors for peri-implantitis are generally gathered under four categories: lesions of peri-implant attachment, presence of aggressive bacteria, excessive mechanical stress, and corrosion. If only one of these factors would start a chain reaction leading to lesions, then the other factors may combine to worsen the condition. With other words, peri-implantitis is a general term dependent on a synergy of several factors, irrespective of the precise reason for first triggering off symptoms.

KEY WORDS: dental implant, osseointegration, peri-implantitis, titanium surface

INTRODUCTION

The long-term predictability of osseointegrated implants has been widely documented.[1] Implantology is a multiclinical discipline: surgery, periodontology, prosthodontics, and biomaterials sciences. Pathologies associated with peri-implant tissues bear the sign of this diversity. Peri-implantitis is a live example of a multifactor pathology, the origin of which being related to many risk factors and where treatment requires a precise and systematic analysis of all the parameters interfering with the integration of the implant.

The objective of this article is not to review in details all the factors potentially associated with peri-implantitis. Hypotheses abound while certainties remain scarce. Our objective therefore, will be to synthesize proven risk factors that may challenge an implant, to itemize the biological mechanisms following multifactor triggering of peri-implantitis, and to describe the physicochemical changes of contaminated titanium surfaces.

Hence, we attempt to analyze various treatments under consideration within a clear and critical manner. Several procedures have been described for the treatment of the inflammatory reaction and the resulting bony defect associated with infection of the peri-implant tissues, including antimicrobial therapy, resective or regenerative procedures.[2–4] Optimal treatment of peri-implantitis must include regeneration of lost bone in direct contact with the implant surface previously exposed to bacterial products. Clinical studies using guided bone regeneration for the treatment of peri-implantitis defects present inconclusive results.[2,3,5] However, peri-implantitis, representing a pathological response, shows specificities considerably limiting our therapeutic options.

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WHAT IS PERI-IMPLANTITIS?

Peri-implant pathologies comprise all inflammatory lesions appearing around functioning dental implants.[6–8] The two principal phenomena are *mucositis* and *peri-implantitis*. On the one hand, mucositis is characterized by the appearance of an inflammation limited to the peri-implant mucosa and reversible in case of appropriate treatment.[9] On the other hand, peri-implantitis is characterized by a loss of supporting bone, both clinically and radiographically proven associated with an inflammatory reaction of the surrounding soft tissues.[8]

The term *peri-implantitis* was introduced in the 1980s[10] to describe a destructive inflammatory process affecting the soft and hard tissues around osseointegrated implants, leading to the formation of a peri-implant pocket and loss of supporting bone. A *peri-implantitis* defect usually assumes the shape of a saucer around the implant and is well demarcated. Because the bottom part of the implant retains osseointegration, bone destruction may proceed without any notable signs of implant mobility until osseointegration is completely lost. The inflammation of the soft tissues is associated with bleeding after gentle probing with a blunt instrument. There may be suppuration from the pocket. Swelling and redness of the marginal tissues are not always very prominent, and there is usually no pain associated with *peri-implantitis*.[8]

Clinical and radiological tests are sometimes difficult to carry out.[11] Probing must be done without forcing the peri-implant pocket tissue, and considerable gum thicknesses around the abutment connection are often normal. Radiographs must be performed with a good angulation and would give support to a peri-implantitis diagnosis only when the progress of the pathology is sufficient and the osseous lesions are quite significant. Buccal and lingual osseous lesions are not detectable by this kind of tool.

Biochemical and bacteriological markers are sometimes used to validate the diagnosis of peri-implantitis[11,12]: peri-implant fluid and bacteria can be taken from the sulcus and analyzed. The heat and flow of peri-implant fluid may also serve as markers of inflammation. However, these tools are still difficult to handle and to correlate.

Peri-implantitis exists only in implants where interface with bone is made functional, which allows to differentiate it from other inflammatory symptoms leading to peri-implant osseous destruction[8]: this is particularly the case of implant losses during the initial phases of the osseointegration. Such events may be due to a poor implant bone quality (resulting in unsatisfactory primary stability; overloading),[13] or to an unsuitable surgical technique. In this last case, the cause can be either bone overheating, leading to an osseous necrosis, or implant surfaces contamination during surgery (with bacteria or residual Malassez epithelial cells), which leads to the development of an apical lesion (wrongly termed "apical peri-implantitis").[14]

Some authors try to assimilate or *carbon-copy* peri-implantitis on a model of periodontitis. However, an implant is not a living tissue. It does not function via a complex interplay of ligament and anchoring interface (cement, lamina dura). It is maintained by osseointegration, that is a phenomenon of interface compatibility between a biomaterial (usually c.p. titanium) and a calcified tissue (bone).[15] Periodontitis, on the one hand, is a peridental ecosystem pathology, a disease maintained by inflammatory imbalances caused by infectious and mechanical risk factors. Peri-implantitis, on the other hand, is actually an osseointegration pathology.

TRIGGERING FACTORS AND INTRINSIC MECHANISMS TO PERI-IMPLANTITIS: FROM ETIOPATHOGENY TO LOSS OF OSSEOINTEGRATION

Triggering factors for peri-implantitis are generally gathered under four categories: lesions of peri-implant attachment, presence of aggressive bacterial *strains*, excessive mechanical stress, and corrosion. If only one of these could starts a chain reaction leading to lesions, then they generally play the role of worsening factors each for the others. It is a synergy of these factors, which will be at the origin of osseous destructions gathered under the term "peri-implantitis."[16]

Peri-implant soft tissues act as a protection barrier for bone tissues sustaining the implant.[17] But this barrier against external aggressions is fragile.[18] Thus, in the event of attachment lesion, bacterial contamination will very quickly reach the bone.[19] The concept of platform switching,[20] by creating a distance between the prosthetic part and the osseointegrated interface of the implant, could make it possible to slow down the lesion and the contamination of peri-implant biological space.
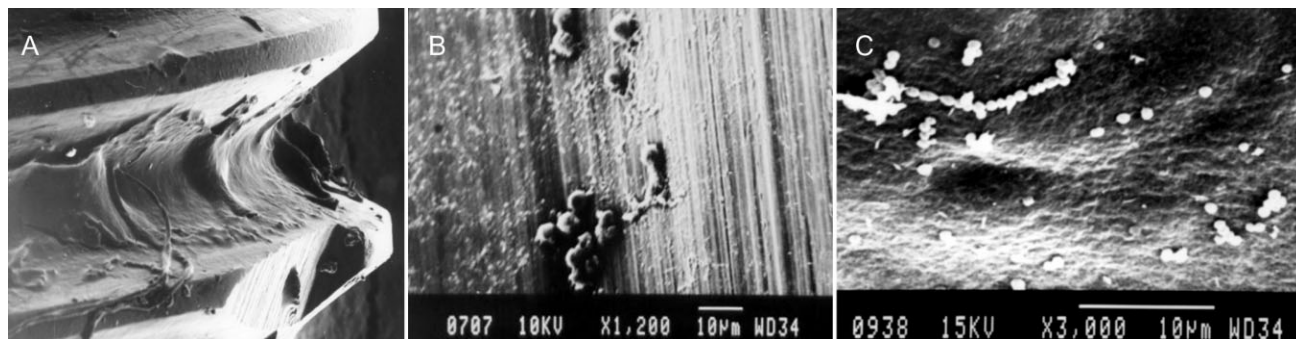
Figure 1 Contaminated implant surface. *A,* Low magnification; macroscopic contamination showing organic remnants sticking between implant threads. *B* and *C,* Higher magnifications; microscopic contaminants (bacteria).

Bacterial colonization of peri-implant pockets is part of initial mechanisms of peri-implantitis (Figure 1). Micro-organisms most frequently associated with implant failures are the rods and mobile forms of Gram-negative anaerobes (*Prevotella intermedia, Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Bacteroides forsythus, Treponema denticola, Prevotella nigrescens, Peptostreptococcus micros and Fusobacterium nucleatum*).[21–23] This type of peri-implant contamination will be particularly fast among partially toothless patients showing an active periodontal disease: colonization of peri-implant sulcus by these microorganisms is effective from the first month following the connection of the implant to its prosthetic part.[24] However, this contamination does not allow for prediction of the appearance of a peri-implantitis. The bacterial populations found in peri-implant space are often very different from those that develop in the sulcus of adjacent teeth.[25]

Peri-implantitis would, according to this diagram, result in an imbalance between the microbial flora and the peri-implant tissues.[26] This concept is illustrated in clinical situations where the peri-implant site is considerably disturbed by ill-balanced diabetes, long-term corticoid treatments, radiotherapy, chemotherapy, or smoking.

Implants with rough surface may promote the accumulation of plaque when these surfaces are exposed to the oral environment. However, there exists no correlation between these implant surfaces and the selection of aggressive bacterial *strains*.[27,28]

Excessive biomechanical stress may trigger peri-implantitis through a promotion of the initial rupture of osseointegration. When an implant undergoes excessive mechanical axial or lateral constraints, microfractures appear in the bone all along the bone implant interface. If sometimes these constraints lead to the fracture of the prosthetic elements, or even of the implant, they will generally be at the origin of a rupture of the osseointegrated interface. This triggering factor of peri-implantitis is thereafter worsened by the inevitable bacterial contamination of the broken interfaces and the appearance of a granulation tissue to the detriment of bone tissue.[26]

The biomechanical stress can be simply related to excessive occlusions of the implant prosthesis. In general, the presence of natural antagonistic teeth or parafunctions such as bruxism constitute the most difficult risk factors to control. Other biodynamic parameters must also be taken into account as of the beginning of the treatment: homogeneous distribution of a sufficient number of implants, reasonable use of cantilever prostheses and removable prosthesis stabilization bars, real passivity of the metal reinforcements, or even restriction of the clinical heights for crowns in accordance with the implants lengths (what often leads to preimplant bone grafting in order to reconstitute resorbed alveolar crests). The quality of the supporting bone will also play an important part in the evolution of osseointegration against an excessive mechanical stress, which would perhaps explain why peri-implantitis is more frequent in the maxilla rather than in the mandible.

Broadly speaking, implant and prosthetic design influence, at all levels, the risk of peri-implantitis: while a precise prosthesis helps limit the accumulation of peri-implant plaque, an adequate distribution of implants of sufficient diameters contributes to a better distribution of the mechanical constraints.

Finally, corrosion is sometimes regarded as a secondary triggering factor. It could cause peri-implantitis

if a base metal alloy is used in direct connection to titanium implant. In these cases, macrophage accumulations were noticed in the peri-implant tissues, which could contribute to the destruction of bone tissue without intervention of a bacterial pathogenic flora.[29] Actually, it is extremely difficult to justify the appearance of a peri-implantitis for this sole reason, because the scales of theoretical potentials of oxido-reduction in biological environment *in vitro* and finally *in vivo* vary considerably; and base metal alloys do not necessarily seem more harmful than those made of precious metal, at least from this point of view.

Peri-implantitis, an osseointegration pathology, cannot be abridged to the sum of its triggering factors. Its specificity comes from the radical transformations of implant and osseous interfaces which, strictly speaking, constitute the biological and physicochemical mechanisms of this pathology. Corrosion is thus much more than a mere triggering factor: it is the phenomenon underlining osseointegration,[30] and hence peri-implantitis.

PERI-IMPLANTITIS: A PATHOLOGY OF OSSEOINTEGRATION

In order to understand the mechanisms of peri-implantitis, it is necessary to define what we generally call "biocompatibility" and what we particularly term "osseointegration." An ideal implant material is to have a chemically dynamic surface, which in turn engenders a histologic interface reaction, akin to that expected in implant absence.[31] On a broader level, biocompatibility is the capability of a material to safely act with an appropriate host in specific applications. Biomaterials should have optimal qualities regarding mechanical aspects, physicochemical stability, absence of toxicity and immunogenicity, and should under no circumstance intervene with the normal tissue healing. In a more specific way, biocompatibility is the material exploitation of host proteins and cells so as to get maximum specific tissue response.[32,33]

Titanium oxidation constitutes the principal reason of its excellent biocompatibility: Ti oxide can pacify tissue-destroying agents immediately after surgical trauma inherent to implantation.[30,34,35] The original theory of osseointegration rested on the passivation of implant titanium surface.[33] Nowadays, nonmetal implants are known to result in osseointegration too.

Oxidative stress is a natural phenomenon associated with ageing. It is at the origin of the production of free radicals (in particular, hydroxyl groups OH°), which, through interacting, can generate oxygenated derivatives (hydrogen peroxide H_2O_2, superoxide radicals O_2^- and O_2^{2-}). In the event of an aggression, the granulocytes are attracted to the site to constitute a first natural defense against viruses and pathogens. They will produce oxygenated derivatives, mainly hydrogen peroxide H_2O_2, in order to destroy the source of the aggression. In case of a conventional wound, this phenomenon remains fairly limited, and the H_2O_2 moderate concentrations are not toxic for the organism because the oxygenated derivatives are quickly deactivated by the cellular catalases. Contrarily, in the event of introducing of a foreign body, such as a biomaterial implant, the free radicals and the oxygenated derivatives are much more concentrated, thus becoming a toxic, and this is called "the foreign body reaction."[30,35] Hydrogen peroxide H_2O_2 will then be lysed in hydroxyl OH° radicals and superoxides O_2^{2-} and O_2^-. These OH° groups are responsible, among other things, for tissue destruction and fibroblastic path induction (at the origin of the pseudoarthrosis). They contribute to orient the mesenchymal osteogenic cells present in the implant site towards a fibroblastic phenotype, to the detriment of the natural osteoblastic way (preosteoblast, osteoblast, and finally osteocyte).

In parallel, this overproduction of H_2O_2 against implant foreign bodies allows the thickening of the titanium oxide layer (TiO_2) on the implant surface. The superoxide radicals O_2^{2-} et O_2^- are incorporated in the implant surface. This thickening of the titanium oxide porous layer allows the incorporation of calcium ions and phosporus of the osseous matrix.[33] H_2O_2 biological oxidation starts upon implantation.[36] The thickening of the titanium oxide layer and the incorporation of bone calcium and phosphorus ions within this layer are phenomena that continue naturally during the entire life of the implant. The establishment of this dynamic interface between the bone and the "foreign body" forms the background to osseointegration of the implant.

In humans, the titanium oxide layer of a dental implant goes from 50 to 2,000 Å in 6 years of osseointegration. During the first 3 months of osseointegration, the titanium oxide layer triples in thickness.[37,38] However, this layer thickens much more quickly in a medullary rather than in a cortical bone: a medullary bone will be better vascularized, and thus the

accumulation of oxygenated derivatives in reaction to foreign bodies will be more significant.[39,40] Inversely, the analysis of failed implants at the second stage of surgery or after 8 years of functioning highlights a titanium oxide layer identical to that of the first days of osseointegration, or even less thick.[41,42]

Thus, peri-implantitis seems associated with a disappearance of the biocompatible interface formed by the implant surface titanium oxide layer (TiO_2). This deosseointegration would be related to the presence of surface contaminants, making impossible the adsorption of oxygenated derivatives and osseous glycoproteins on the implant surface.[43] Indeed, the cleaner the biomaterial surface, the greater is its surface energy; the more important the biomolecule absorption, the more favorable is adhesion of cells. One single layer of contaminants is sufficient to make a biomaterial unusable.[43–45] What is then the nature of the contaminations partaking in the physicochemical mechanisms of peri-implantitis? Are we talking about contaminations on the cellular, molecular, or atomic level? On this answer will depend the nature of possible treatments from a scientific viewpoint.

CORROSION AND CONTAMINATIONS: HOW TO INVESTIGATE PATHOLOGICAL EQUILIBRIUM OF PERI-IMPLANTITIS

In order to analyze with precision the composition of the implant surface during osseointegration and peri-implantitis, two main technologies are usable. X-ray photoelectron spectroscopy (XPS) remains one of the best tools for surface chemical composition. Auger electron spectroscopy (AES) is also useful for elemental surface composition and concentration depth profile analysis (Figure 2). Moreover, XPS and AES give an interesting appreciation of oxide thickness. Further information could be obtained by secondary ion mass spectrometry, energy-dispersive x-ray analyses, and nuclear microprobe analysis.[45] Thus, these techniques make it possible to obtain the quality profiles of titanium oxide.[15,45,46]

Of all the alloys used in dentistry, titanium remains one of the most difficult materials to understand. It naturally possesses the redox potential, which is by far the lowest among all dental alloys. However, in the organism, in contact with acids, bases, enzymes, and bacteria, it continues to be the most difficult alloy to corrode (Figure 3).
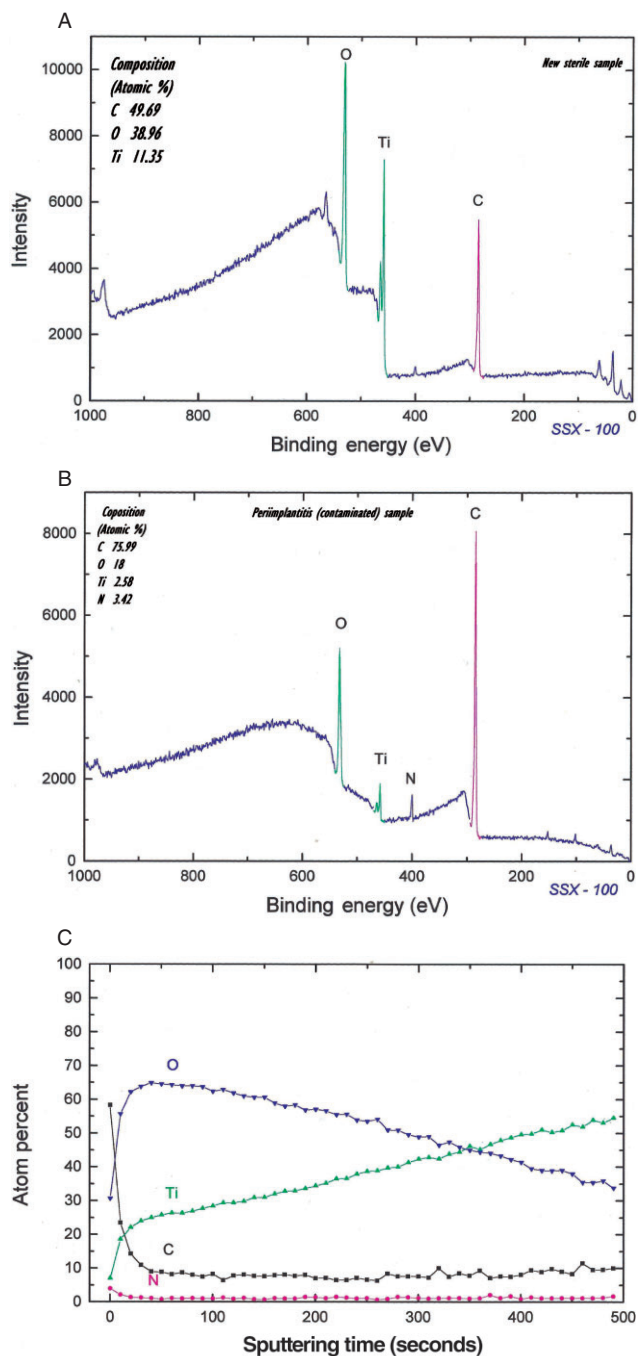

Figure 2 X-ray photoelectron spectroscopy (XPS) of an unused implant showing only C, Ti, and O signals (A). (B) XPS spectrum of a failed contaminated implant, C signal is very high compared with Ti and O, and traces of N were also detected. Depth profile analysis can give an idea about Ti oxide thickness by the situation of the crossing point between O and Ti curves (C).

Implant surface contamination triggers a chain reaction leading to the dissolution of the titanium oxide layer and making its natural reconstitution impossible. Organic contaminants accelerate the reaction to foreign
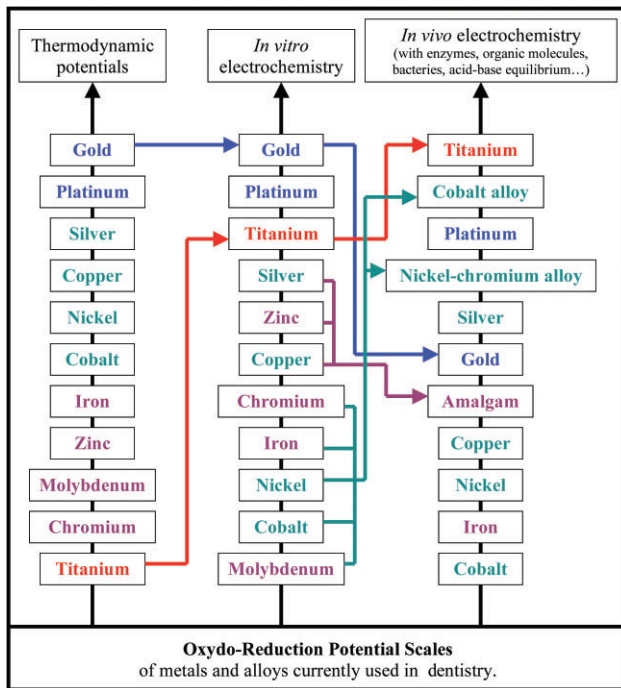
Figure 3 Oxido-reduction potential scales of metals and alloys currently used in dentistry. Ti has a poor oxido-reduction potential compared with other metals, but seems to be the highest in presence of acids, bases, enzymes, and bacteria.

bodies and the production of free radicals: $O_2 + 2H_2O + 4e^- \rightarrow 4OH^-$. The production of these free radicals is linked to the reaction of implant surface titanium dissolution according to the equation $Ti \rightarrow Ti^{4+} + 4\,e^-$.[34] The contamination thus induces an accelerated corrosion and a massive release of titanium ions.[47] It is the mechanism underlying the peri-implantitis of bacterial origin.

Peri-implantitis may additionally be caused by excessive mechanical constraints. In effect, following passivation of the implant surface, the titanium oxide layer (TiO_2) can be considered as a relatively fragile ceramic prone to microfractures emanating from overloading. A repair naturally occurs, thus rebuilding titanium oxide structures by means of catching blood oxygen species circulating both in the surrounding bone and the soft tissue. However, should the phenomenon remain continuous as in clinical overload situation, the area of the implant subjected to mechanical stress will lead to a Ti dissolution as a result of the Ti oxide layer destruction. This phenomenon initiates an accelerated corrosion and a release of titanium ions.[48]

Most ailing implant cases show a circumferential bone resorption (typical U crater, Figure 4A). The bottom of this pocket mostly corresponds to the apical end of the abutment screw. Biomechanically, this represents the weakest part of the complex implant–abutment–crown, while an abnormal overload will accordingly have its bending moment on this area. Furthermore, it has been noticed that most implants when they come to break, it is always up to this line (Figure 4B). Signs of corrosion have been observed on the soft tissue surrounding a broken implant (Figure 4C). On this particular case, a burr was needed to remove the nonmobile apical part of the broken fixture (Figure 4, D and E) still looking osseointegrated, since hard tissue debris still clings to the threads (Figure 4F). SEM (scanning electron microscope) examination has shown a structure similar to bone (Figure 4G), while light microscopy has revealed a dense fibrous tissue (Figure 4, H and I).

Equally, SEM and XPS analyses have been conducted on a retrieved implant unscrewed due to bone resorption, itself a result of deep peri-implantitis. On those typical dark spots hardly visible with the naked eye (Figure 5A), XPS can reveal a predominant signal of C instead of Ti and O normally present on an undestroyed surface; observations as in accordance with the findings of many authors (Figure 5B). Based on these two cases then, we learn the following:

1. Even if we can treat the peri-implantitis problem from a surgical (filling and regenerating technique), microbiological, or biomechanical standpoint, and even though we succeed to detoxify the Ti surface, how can we clinically make sure the corrosion has not already been effective?
2. When everything is done properly, how can we be positive that the remaining bone, radiographically good-looking and even perfect to the naked eye, is not already decalcified and also not more than a dense fibrous tissue?

Consequently, the challenges posed by peri-implantitis treatment are at the same time numerous and very complex. All therapies should lead to an effective contaminant eradication, an unaffected implant topography, and a reestablishment of initial surface atomic composition and oxide structure, with no lethal effects on surrounding tissues. *This last point is vital to the preservation of the osteogenic potential for the sake of an eventual regeneration.*
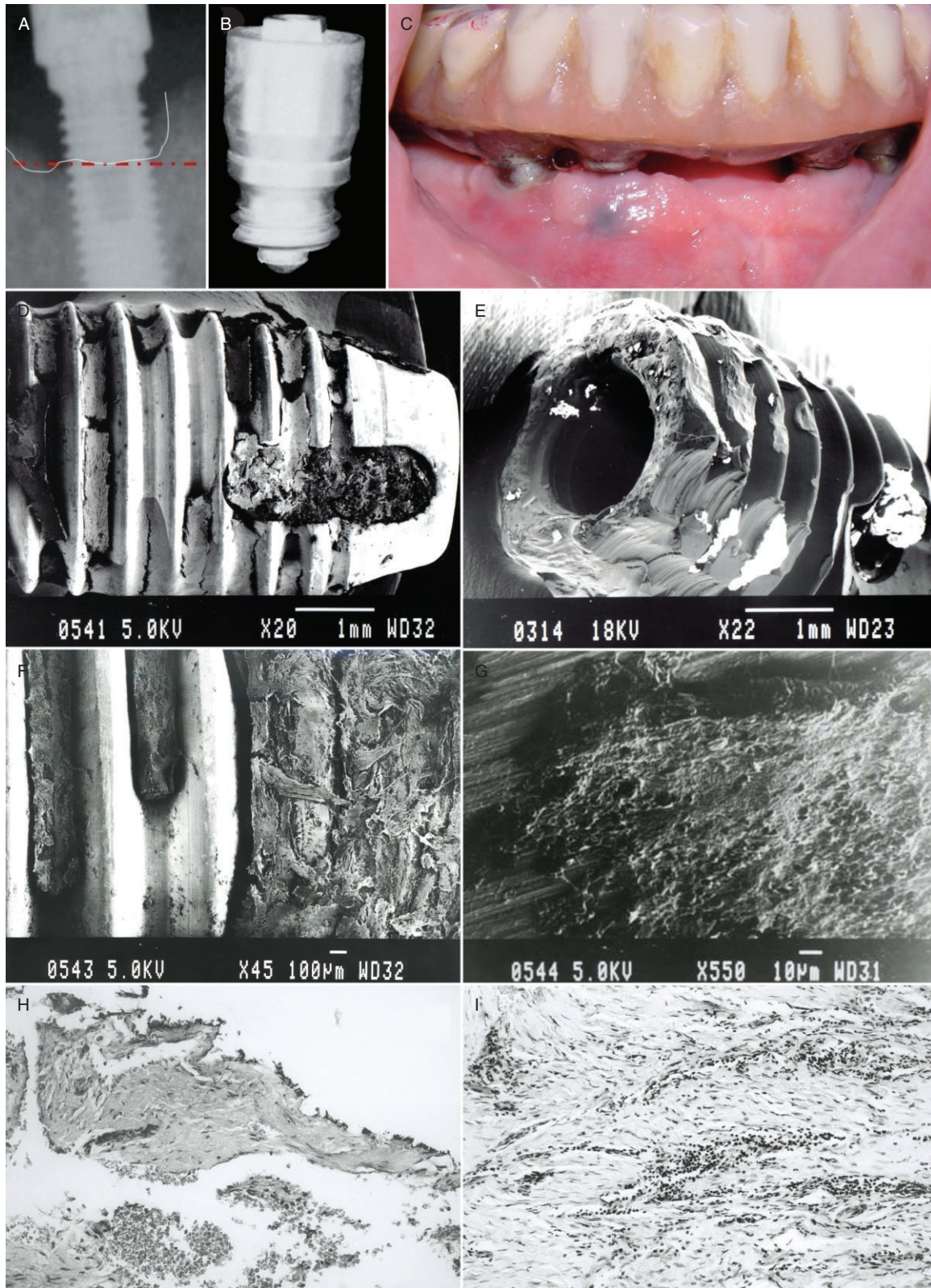
Figure 4 During peri-implantitis, a typical circumferential bone resorption (U crater) appears around implants (A), and the bottom of this crater is often on the line of implant break and correspond to the extremity of abutment screw (the weakest part of the complex implant–abutment–crown) (B). Signs of corrosion are easily observed on the soft tissue surrounding a broken implant (C). A burr is often needed to remove the nonmobile apical part of a broken fixture (D,E) still looking osseointegrated with hard tissue attached to the implant surface (F). Scanning electron microscope examination shows a bone-like structure (G), while light microscopy reveals in fact a dense fibrous tissue (H,I).
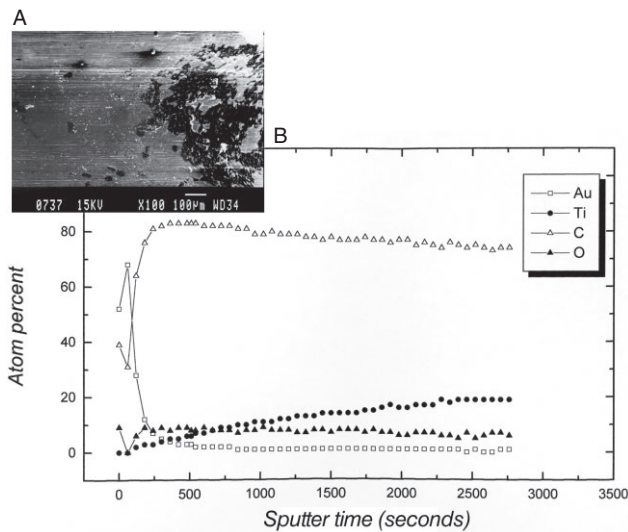
Figure 5 Scanning electron microscope (A) and x-ray photoelectron spectroscopy (XPS) (B) analyses on a retrieved implant due to deep peri-implantitis. On the typical dark spots (A), XPS can reveal a predominant signal of C instead of Ti and O (B) normally present on a clean surface. This is a typical sign of deep surface corrosion.

CORROSION AND CONTAMINATIONS: FROM SYMPTOMATIC THERAPEUTICS TO THE GLOBAL TREATMENT OF A PATHOLOGICAL EQUILIBRIUM

Many protocols were suggested for the treatment of peri-implantitis. The majority seeks the decontamination of the implant without really taking into account the problem of physico-chemical modifications of the de-osseointegrated interface. The concept of these decontaminations relies on an association of a mechanical cleaning via microabrasion and an antiseptic chemical treatment, in general just before guided bone regeneration:[49] prophy-jet and chloramine T 1%,[50,51] prophy-jet and citric acid,[52] air-powder abrasive, chlorhexidine and citric acid,[53] Delmopinol (detergent),[54,55] CO_2 laser alone.[56]

None of these treatments was regarded as completely satisfactory. If some authors expected to treat human peri-implantitis with their proposed protocol,[52] no tangible scientific proof (starting with an analysis of the physicochemical condition of the treated implant surface) was provided by these studies.

Starting from a sound understanding of the perturbation of the interface at the origin of contamination and peri-implantitis, some studies were conducted in view of developing a treatment allowing the physico-chemical reestablishment of an osseointegratable implant surface. Peri-implantitis is an osseointegration pathology; therefore, an interface pathology: all protocols aiming to treat it must be evaluated using reliable techniques of analysis, such as SEM and XPS.

A first study[57] evaluated six chemical and physical techniques for the cleaning of contaminated titanium surfaces on clinically failed and retrieved implants by means of SEM and XPS as compared with unused controls. The six different techniques were: (1) rinsing in absolute ethanol for 10 minutes; (2) cleaning in ultrasonic baths containing trichloroethylene (TRI) and absolute ethanol, 10 minutes in each solution; (3) abrasive cleaning for 30 seconds; (4) cleaning in supersaturated citric acid for 30 seconds; (5) cleaning with continuous CO_2 laser in dry conditions at 5 W for 10 seconds; and (6) cleaning with continuous CO_2 laser in wet conditions (saline) at 5 W for 10 s. SEM of failed implants showed the presence of contaminants of varying sizes, and XPS showed almost no titanium but high carbon signals. XPS of unused titanium implants showed lower levels of titanium as previously reported, probably due to carbon contamination, which increased with time in room air. Cleaning of used implants in citric acid and rinsing with deionized water for 5 minutes, followed by cleaning in ultrasonic baths with TRI and absolute ethanol, gave the best results with regards to macroscopical appearance and surface composition. However, as compared with the unused implants, the results from an element composition point of view were still unsatisfactory. Drawing toward the end of this comprehensive study, it would seem necessary to conclude that further development and testing of techniques for cleaning of organically contaminated titanium is needed.

Starting from these initial results, a therapeutic protocol corresponding to the logic of interface treatment was taken into consideration. This therapeutic solution associates chemical and physical processes in order to decontaminate the implant surface while reestablishing a surface compatible with osseointegration.[58,59] This requires three stages:

1. vaporization of bacterial and inflammatory debris by means of CO_2 laser;
2. citric acid application to detach burnt remnants from titanium (rinse generously); and
3. H_2O_2 application (as an oxygen source), which will be evaporated in situ with CO_2 laser beam.

CO_2 laser is already well known in periodontology. Its main indications are inflammatory soft tissue evaporation[60–62] and titanium surface decontamination and sterilization.[56,59,63–65] In order to avoid overheating during surface decontamination of titanium implants using CO_2 laser, we recommend the use of specific physical parameters. A previous study shows that the CO_2 laser when used on a wet implant surface in a pulsed mode at 8 W/10 ms/20 Hz during 5 seconds induces a temperature increase of less than 3°C.[66] This would minimize the risk of temperature-induced tissue damage as a result of lasing implant surfaces.

Citric acid treatment for 30 seconds, followed by a minimum of 2 minutes rinsing with distilled water, result in a clean surface. Interestingly, the recommended period of rinsing after citric acid treatment (30 seconds)[52] results in large nonreflecting areas corresponding to remained acid traces; when continuing the rinsing of the same implant for about 2 minutes, these areas disappear completely.[57] This need of a generous rinsing can be explained by the fact that Ti oxide reacts chemically like an amphoteric substance, which means that it can act like a base in the presence of an acid and like an acid in the presence of a base.[58]

The use of hydrogen peroxide H_2O_2 evaporated on titanium surface using CO_2 laser relates to a simple physicochemical concept. H_2O_2 is quickly adsorbed on a titanium implant surface.[67,68] The use of a powerful oxidizer such as H_2O_2 and the laser-induced heat makes it possible to accelerate considerably the exchanges in titanium and oxygen atoms through the surface layer of titanium oxide. Hence, the titanium oxide layer thickens quickly, which enables it to become an osseointegratable surface upon ending the surgery.[15,43,44,46]

The development of the titanium oxide layer depends more on hydrogen peroxide decomposition speed rather than on its basic concentration.[48,69] For this reason, it is more desirable to use nontoxic low concentration of H_2O_2 and activate its decomposition through CO_2 laser-induced temperature increase. The required reaction $(2H_2O_2 \rightarrow 2H_2O + O_2)$ presents an enthalpy $\Delta H = -99$ kJ/mol. A surface temperature of at least 80°C will thus be sufficient to activate hydrogen peroxide H_2O_2 on treated implant surfaces.

A complete scientific investigation was conducted[58] to evaluate the efficacy of different combinations of these chemical and physical methods (citric acid, hydrogen peroxide, and CO_2 laser treatment) for removal of contaminants and subsequent reconstruction of the surface oxide of intraorally contaminated titanium foils. Commercially pure titanium foils (99.6%, 5×5 mm in size) were contaminated by placement on dentures in volunteering patients, simulating a peri-implantitis situation. The contaminated foils and clean control foils were treated by seven and six combinations of citric acid, hydrogen peroxide, and CO_2 laser irradiation, respectively. The effect of the cleaning procedures was evaluated by XPS and SEM.

The initial elemental composition of the contaminated foils was 70% carbon (C), 20% oxygen (O), 10% nitrogen (N), and only traces of titanium (Ti) (<1%). One treatment proved to be more effective than the others: irradiations by 5-second cycles of superpulsed CO_2 laser at a power of 7 W, 10-millisecond pulse width, and with an 80-Hz frequency on a wet surface, to vaporize bacteria and inflammatory soft tissue debris, followed by repeated application of supersaturated citric acid for 30 seconds, each time followed by rinsing with ultrapure water for 2 minutes until all burnt tissue remnants had been removed. Finally, hydrogen peroxide of 10-mM concentration was added to the implant surface and evaporated by CO_2 laser at the same settings (Figure 6). This treatment protocol resulted in 10% Ti, 45% O, 41% C, and 2 to 3% N, a composition comparable with that of unused foils: 9% Ti, 40% O, 48% C, and traces of N and chlorine (Cl). XPS profiles showed that the thickness of the surface oxide was restored and even augmented with this protocol for treatment of contaminated titanium.

This protocol seems to be effective for cleaning and reestablishment of the atomic composition and oxide structure of contaminated titanium surfaces.

A first *in vivo* study was carried out on beagle dogs[70]; the aim of this study was to examine the use of CO_2 laser in combination with hydrogen peroxide in the treatment of experimentally induced peri-implantitis lesions. Three dental implants were placed in each side of the edentulous mandible of four beagle dogs. Implants with a turned surface and implants with a sandblasted large-grit acid-etched (SLA) surface (SLA, Straumann® AG, Waldenburg, Switzerland) were used. Experimental peri-implantitis was induced during 3 months. Five weeks later, each animal received tablets of amoxicillin and metronidazole for a period of 17 days. Three days after the start of the antibiotic treatment, full-thickness flaps were elevated, and the
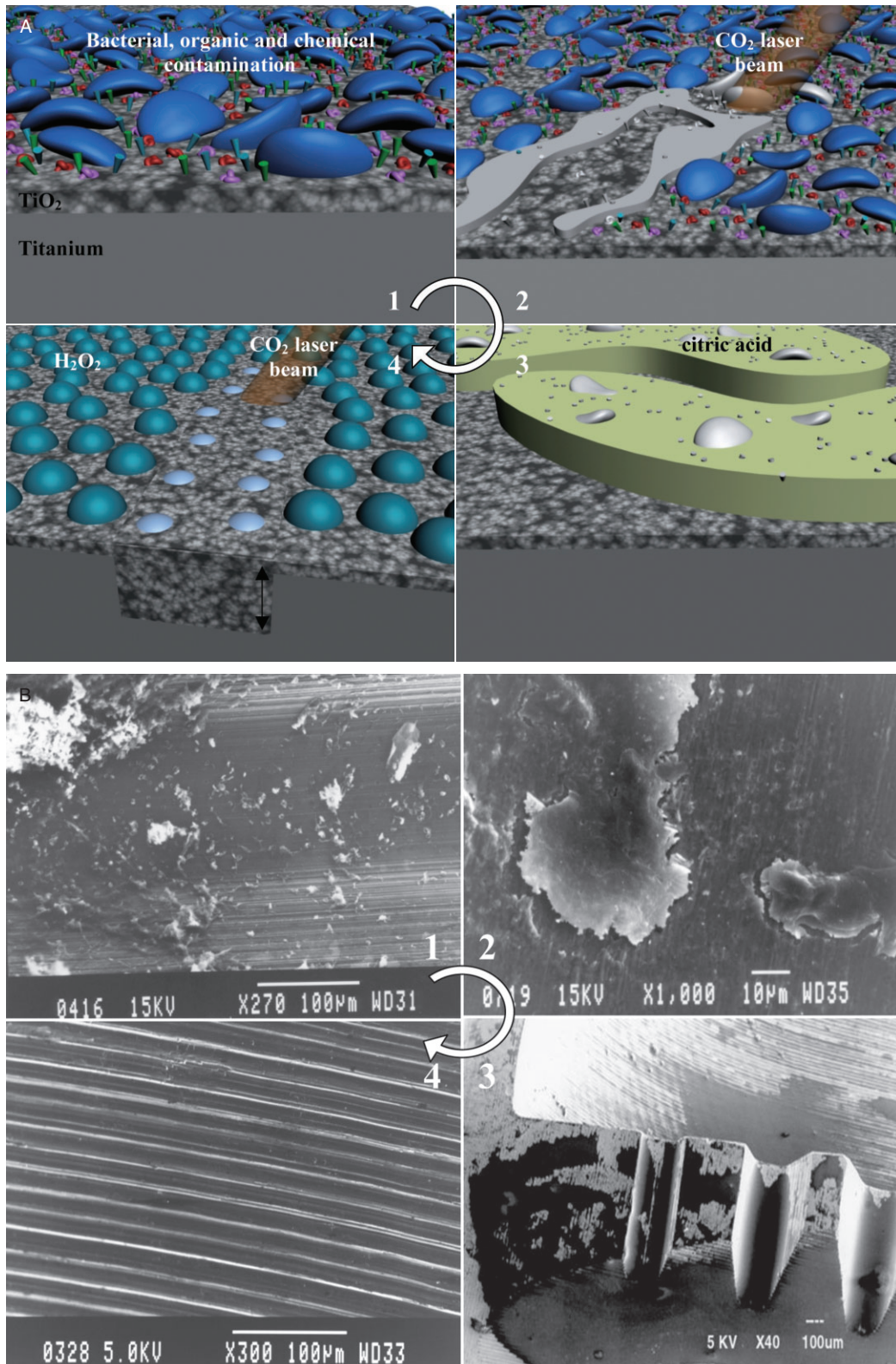
Figure 6 Schematic view (*up*) and related SEM pictures (*down*) of a potential efficient surface treatment after peri-implantitis. Implant surface is contaminated (1) by bacteria (*blue*), organic components (*red* and *pink*) and corrosion substrates (*green*). Titanium oxyde layer is partially destroyed and thin. Implant surface is treated using CO_2 laser beam (2). Laser dehydrates and detaches organic contaminants (bacteria, blood cells, fibrous tissue) from the surface, which facilitates its elimination by citric acid (3). Re-establishment of the atomic composition of the oxyde (TiO_2) is performed by mean of hydrogen peroxide as an oxygen source, activated by a CO_2 laser beam (which is used as a localized heat source), and the oxide layer of the implant surface thus becomes thicker (4).

granulation tissue in the bone craters was removed. In the two anterior implant sites in both sides of the mandible, a combination of CO_2 laser therapy and application of a water solution of hydrogen peroxide was used. The implant in the posterior site of each quadrant was cleaned with cotton pellets soaked in saline solution. Biopsy specimens were obtained 6 months later. The amount of reosseointegration was 21 and 82% at laser-treated turned-surface implants and SLA implants, respectively, and 22 and 84% at saline-treated turned-surface implants and SLA implants, respectively.

This study demonstrated three important points:

1. A combination of systemic antibiotics and local curettage and debridement resulted in the resolution of experimentally induced peri-implantitis lesions; however, this experimental peri-implantitis is perhaps not the best model, due to the specific metabolism of dogs.
2. At implants with a turned surface, a small amount of reosseointegration was observed, whereas a considerable amount of reosseointegration occurredat implants with an SLA surface; some previous studies seemed to have already gone in this direction.[36]
3. The use of CO_2 laser and hydrogen peroxide during surgical therapy had no apparent effect on bone formation and reosseointegration. However, in this study, citric acid was not used for the removal of remnants before hydrogen peroxide and CO_2 laser application. We can also conclude that there is no possibility to reestablish the atomic composition by mean of peroxide activated with CO_2 laser, since the Ti surface is not perfectly and microscopically cleaned.

Further investigations are thus required to validate the ideal protocol for the treatment of peri-implantitis in humans.

DISCUSSION: FROM THE GLOBAL TREATMENT OF A PERI-IMPLANTITIS PATHOLOGICAL EQUILIBRIUM TO A NEW PHYSIOLOGICAL PERI-IMPLANT BALANCE?

Among the numerous protocols in the literature, several are effective for the elimination of inflammatory residues and bacterial contaminations, but none is 100% bound to provide a real reosseointegration. If the protocol we propose incontestably allows a wholesome

treatment of the osseointegratable surface, the problem of osseous lesions construction will perdure. There exist probably two options.

If the osseous lesion shows walls, a guided bone regeneration protocol is an option, provided that the implant surface is treated according to our protocol, and that bone defect sizes are limited. In this situation, the possible damages, induced by surface treatment (citric acid, hydrogen peroxide, and laser heat), can make such option hazardous.

The reconstruction of the destroyed parts will often be carried out using bone graft materials, associated sometimes with antibiotics and/or platelet concentrates. These therapies must still be evaluated with precision. However, it is already possible to launch several fields of research.

Any material for bone filling should be as hydrophilic as possible, and that for two main reasons: a hydrophilic material is naturally bacteriostatic,[71] which allows to limit its possible recontamination. Moreover, one such material will easily absorb an antibiotic solution or a platelet concentrate. By and large, all aqueous additives will be easily incorporated in the biomaterial matrix, which logically increases potential synergies.[72]

The use of antibiotics in graft materials is already widely tested in periodontology,[73] namely with tetracyclines.[74] The use of a hydrophilic biomaterial would allow a better absorption of antibiotic solutions, which would in turn make it possible to have a filling material very hard to contaminate by oral germs. Besides, it should be noted that the use of the antibiotics whose spectrum would more specifically touch anaerobic germs, presumably the most harmful for a bone graft, is an already-mentioned option,[75,76] albeit it still needs further investigation.

Last but not least, the coupling of all these treatments with fibrin products such as platelet-rich plasma or platelet-rich fibrin membranes[77] could yield even more complete results. Fibrin plays a key role all throughout osseous cicatrization and osseointegration in a general way.[78] The release of growth factors from these platelet concentrates could also partake in the acceleration of the initial stages of the reosseointegration.[79]

CONCLUSION

Peri-implantitis cannot be considered as a mere disease of peri-implant tissues. The diagram of periodontal diseases relates to it only very partially. Peri-implantitis is

an osseointegration pathology, and is therefore a pathology of interfaces due to a biocompatibility deterioration.

Various methods have been applied for the treatment of peri-implantitis lesions. It has been reported that the procedures used have been effective in eliminating the inflammatory lesion, but that reosseointegration to the once-contaminated implant surface has been difficult or impossible to achieve.

The treatment that we recommend combines the consecutive use of CO_2 laser, citric acid and evaporated hydrogen peroxide H_2O_2 using CO_2 laser. It is currently the only treatment allowing the decontamination and the reestablishment of the physicochemical osseointegratable architecture of implant surfaces. Yet further studies, as well as serious clinical procedures, are necessary to validate the practicality and the real therapeutic prominence of such peri-implantitis treatment proceedings. In conclusion, it should reiterated that if the treatment of the interface is essential for an osseointegration disease such as peri-implantitis, the means of reconstruction of the destroyed bone tissues also will be equally decisive in obtaining reliable and reproducible clinical results.

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The authors declare no competing financial interests.

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