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# Peri-implantitis is not periodontitis: Scientific discoveries shed light on microbiome-biomaterial interactions that may determine disease phenotype

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## 1 | PERI-IMPLANTITIS IS NOT PERIODONTITIS: CLINICAL OBSERVATIONS

Peri-implantitis is an immune-mediated biological complication that is estimated to affect 12%-24% of dental implants.[1,2] For more than a decade, peri-implantitis was treated with the antimicrobial and mechanical treatments used for periodontitis until it was realized that these treatments were ineffective.[3] They have similar phenotypes when assessed cross-sectionally. Both entities are characterized by the common clinical findings of erythema and edema of the oral mucosa, and histologically appear to be associated with leukocytic infiltration and intense pro-inflammatory signaling.[4] Importantly, periodontal and peri-implant inflammation are associated with the presence of periodontal or peri-implant biofilms, respectively. These seemingly identical phenotypic inflammatory phenotypes that are related to bacterial biofilms led to the assumption that the 2 entities share similar pathogenetic mechanisms.[5,6] This assumption that the pathogenesis of peri-implant inflammatory disease can be based on the pathogenetic mechanisms of periodontal disease appears to be simplistic based on published data.

When implants are affected by peri-implantitis, they present clinically with rampantly progressive inflammatory destruction of the peri-implant bone.[7] As peri-implantitis was first described in the 1990s as an inflammatory, bacterial-related process that leads to progressive bone loss around dental implants, culture-based microbial identification studies were employed that identified known periodontal pathogens as the culprit.[6] Consequently, treatment protocols for peri-implantitis were modeled according to those used for periodontitis. However, existing peri-implantitis treatments only yield short-term benefits, with some interventions showing a disease recurrence rate of up to 100% after 12 months.[3] The lack of efficacy of antimicrobial treatments for periodontal pathogens, coupled with recent discoveries from open-ended microbial investigations, have created a heightened need to revisit the pathogenesis of peri-implantitis compared with that of periodontitis.[8-10]

## 2 | PERI-IMPLANTITIS IS DISSIMILAR TO PERIODONTITIS AND A NEW MODEL OF INFECTION IS REQUIRED

When carefully examined, the progression of inflammatory destructive disease around implants differs from that around teeth. The rate of progression of bone loss around implants is rampant; substantial bone degradation can be seen clinically as early as 6 months following implant placement.[1] Thus far, there is no explanation for the difference between bone loss associated with periodontitis and that found in peri-implantitis. Nevertheless, contemporary culture-free methods for identification of microbes have unveiled a previously unexpected dissimilarity between the microbiome around teeth and that around implants, which could provide an answer to the distinct disease phenotypes.[8] When the observation of a distinct microbial signature in peri-implantitis, different from that in periodontitis, is viewed through the prism of biofilm formation, it only

seems reasonable that the initial bacterial colonizers would also be different because chemically different substrata (metal titanium vs mineralized organic cementum/dentin) will dictate subsequent bacterial accumulation and result in distinct biofilm structures. Surface energy, topography, wettability, and electrochemical charges of substrata all affect biofilm adhesion and formation.[11]

Titanium is a highly reactive metal; when exposed to fluid medium or air, it quickly develops a layer of titanium dioxide. This dioxide layer forms a boundary at the interface between the biological medium and the metal structure. It produces passivation of the metal, thus determining the degree of biocompatibility and the biological response to the implant.[2,12] On the other hand, teeth-bound subgingival biofilms form on mineralized organic substrates primarily composed of collagen and proteoglycans. It is well established that the electrochemical and physicochemical properties of implantable biomaterials affect bacterial adhesion and succession during biofilm formation.[11,13] The salivary pellicle creates a protein rich zone on the implant surface composed of albumin, mucins and other proteins that support initial bacterial adhesion.[14] The differences between implant- and tooth-bound biofilms appear as early as bacterial adhesion commences. The electrostatic forces and ionic bonding that drive initial bacterial adhesion are fundamentally different for titanium dioxide compared with mineralized organic hydroxyapatite.[15] It is now well established that *Streptococcus* spp employ their molecular surface milieu, including adhesins, to colonize implant surfaces almost immediately after exposure to the oral environment.[15-20] While *Streptococcus* spp also have major roles in adhesion to organic dental substrates, the distinct microenvironment created by metal implant surfaces and their local dissolution products appears to dictate a very different ecological succession. For example, on hydroxyapatite, typically adhesion of *Streptococcus* spp is succeeded by *Actinomyces naeslundii*, while on titanium substrates there are significantly lower numbers of *A. naeslundii*, and coaggregation with *Veillonella* spp is observed in early biofilms.[21,22] This argument can be better illustrated using the example of amalgam surfaces versus enamel surfaces. Extensive research supports the finding that despite the direct proximity of amalgam and enamel in amalgam-filled teeth, each surface harbors a distinct biofilm. Amalgam surfaces cultured after inoculation with oral bacterial biofilms exhibit a substantial rise in mercury-resistant strains of bacteria over a period of 48 hours.[23] Strikingly, the genes conferring resistance to mercury were found to colocalize on the same mobile genetic elements that conferred antibiotic resistance, which further explains the antibiotic resistance of biofilms on metal substrates, such as in peri-implantitis.[13]

Each ecological niche is defined by physicochemical and electrochemical characteristics that present a series of challenges with which streptococci and other early colonizers have to contend.[14] These differences affect bacterial adhesion and may enrich for selected taxa. For instance, the wettability properties and adsorption kinetics of the intentionally microrough and hydrophilic implant surfaces are different from those of dentin, which affects the organization of pellicle components.[24] Moreover, the interaction between titanium surfaces and the oral environment leads to increased concentrations of titanium in peri-implant plaque that both interacts with the microbiota[2] and may alter macrophage responses to lipopolysaccharide.[2,25] The end result of these differences is that despite the existence of a core microbiome that includes early colonizers with strong adhesion properties (eg *Streptococcus* spp) and bridging organisms which support complex biofilms (eg *Fusobacterium* spp), the microbial communities are distinctly shaped by each substratum. In a study that assessed the effects of substrata in shaping the local microbiota in vivo, Yu et al[20] included 18 people with both periodontitis and peri-implantitis and collected subgingival and submucosal plaque from either healthy sites or sites with peri-implantitis and inflamed periodontal sulci within the same individual. Following 16S ribosomal DNA sequencing, a total of 5000 distinct operational taxonomic units, but only 31 "core species" (defined as being present in >90% sites), were identified. Thus, it becomes apparent that the peri-implant microbiome is distinct and a new model of peri-implant infection is warranted.

## 3 | THE PERI-IMPLANT MICROBIOTA RESISTS PERIODONTAL ANTIBIOTIC REGIMENS: A TESTAMENT OF UNIQUE FUNCTIONAL SIGNATURES IN PERI-IMPLANT BIOFILMS

As previously discussed, contemporary culture-free methods for microbial identification have unveiled dissimilarities between the subgingival microbiome around teeth and implants that could provide an answer to the aforementioned distinct disease phenotypes.[26,27] A study using 16S RNA sequencing to analyze adjacent peri-implant and periodontal microbiomes in states of health and disease found that 85% of individuals shared less than 8% of abundant species between teeth and implants.[28] Furthermore, peri-implant communities demonstrated less diversity than periodontal microbial communities.[28] The important observation of a distinct microbial signature in peri-implantitis compared with periodontitis[28-30] necessitates research on the capability of the host to mount or potentially resolve an inflammatory response against peri-implant bacteria. While it is likely that the oral taxa that colonize implant biomaterial surfaces originate from dental biofilms, crevicular and extra-crevicular reservoirs. This fact becomes of great importance during ecological transitions from biomaterial-host homeostasis to dysbiosis and adverse biological responses. One additional finding that alludes to the differences between periodontal and peri-implant microbiotas is the resistance of the latter to antibiotic regimens that are efficacious against periodontitis. Hallstrom et al[9] administered azithromycin for 4 days, as an adjunct to nonsurgical debridement, to patients with peri-implant mucositis (ie, inflammation of the peri-implant mucosa). Subjects were followed for 6 months, and the results showed no difference in probing-depth measurements or bacterial composition, as determined by checkerboard DNA-DNA hybridization, between

those who did or did not receive adjunctive antibiotics. Leonhardt et al[10] report the 5-year results from surgical treatment with adjunctive systemic antibiotics for 9 individuals with peri-implantitis. The antibiotic regimen was determined based on susceptibility testing of target bacteria, and the majority of participants received antibiotics, such as tetracycline or amoxicillin plus metronidazole, targeted against putative periodontal pathogens. During the 5-year evaluation period, 42% of the implants included in the study either failed clinically and were lost, or continued to lose peri-implant bone.[10]

Taken together, the findings of resistance of microbial peri-implant communities to beta-lactam antibiotics (which are effective against periodontal communities, even when used as monotherapy),[31] and reduced alpha (within-sample) diversity of microbial communities, strongly suggests that a new model of infection is required (Figure 1). First, low-diversity peri-implant communities are dominated by a few high-abundance species, such as *Veillonella* spp and *Neisseria* spp that are known to produce beta-lactamase enzymes which confer antibiotic resistance. Second, while gram-negative bacteria have the capacity to produce beta-lactamases, peri-implant communities include gram-positive bacteria that are also resistant to beta-lactam antibiotics. Specific gram-positive taxa identified in human peri-implantitis, such as *Streptococcus mitis* and *Streptococcus oralis*, are known to produce low-affinity penicillin-binding proteins; these proteins are antibiotic-binding sites, acquired through gene transfer, that confer high resistance to beta-lactam antibiotics.[32] These observations serve as an example of how the transfer

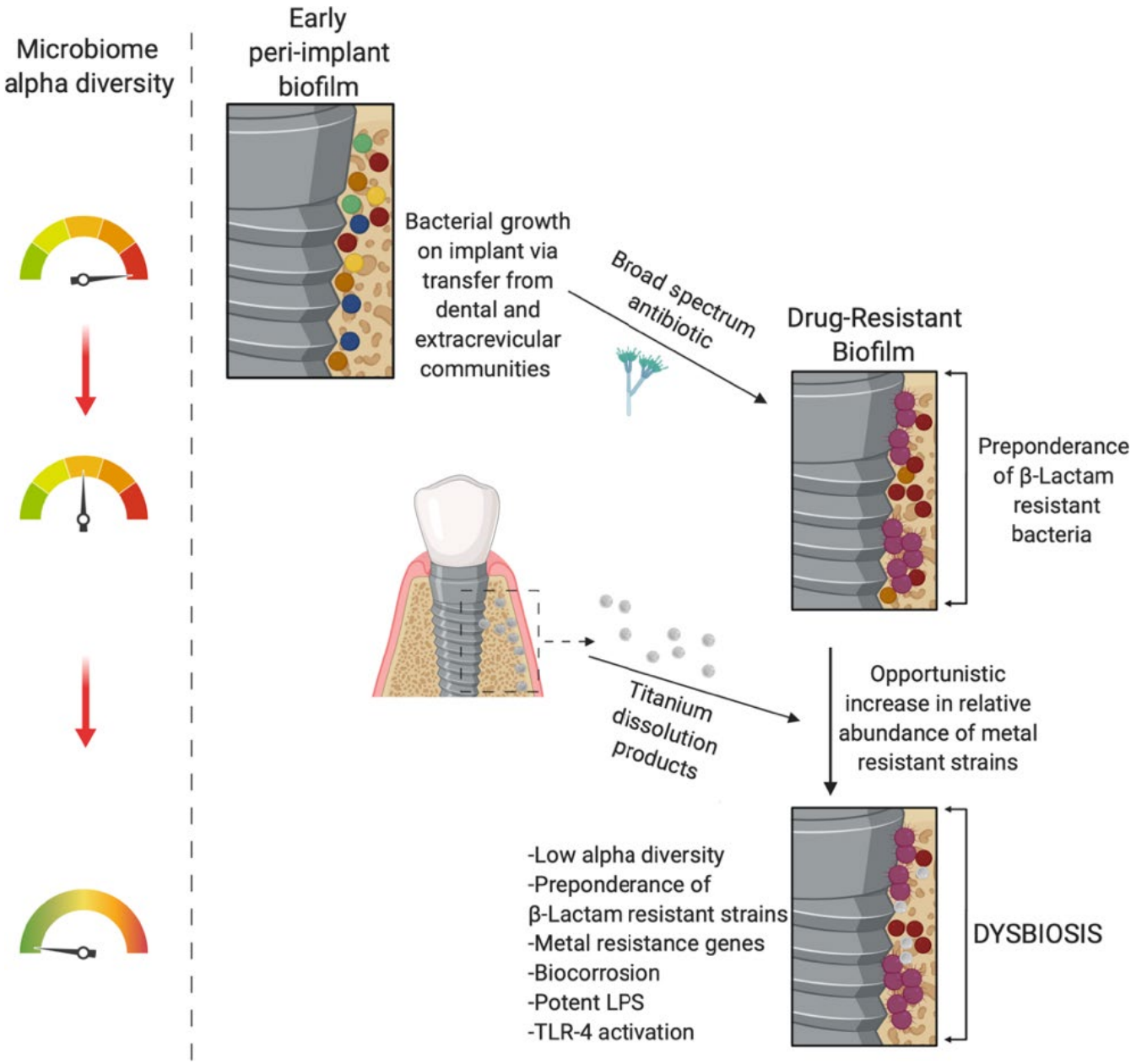


**FIGURE 1** Theoretical model of local and environmental factors that lead to reduced microbiome alpha diversity and dysbiosis in peri-implant disease, as observed by Daubert et al and Dabdoud et al.[8,75]LPS, lipopolysaccharide; TLR-4, toll-like receptor 4 [Colour figure can be viewed at wileyonlinelibrary.com]

of knowledge on the red complex bacteria, important pathogens in periodontitis but not critical in peri-implant biofilms, may carry confirmation bias. It is now well established, from multiple open-ended microbiome investigations, that some of the red complex bacteria may be occasionally encountered in peri-implantitis, but they are much less abundant than in periodontitis and their presence is rare. This may be related to the vast increase of metal ions in the peri-implant sulcus in peri-implantitis and the effect of these metal ions on microbiome profiles.[2] The mechanisms that lead to release of titanium particles into the sulcus and the effects of these particles on the microbiome will be discussed in further detail in the rest of this chapter.

## 4 | FINDINGS OF TITANIUM PARTICLES IN THE TISSUES SURROUNDING TITANIUM DENTAL IMPLANTS

No metal or metal alloy is completely inert in vivo, and because the metallic implant is in contact with tissues and body fluids, ions/particles generated as a result of electrochemical processes (corrosion) can be released into the biological milieu. Ions/particles can also be released as a consequence of wear or friction (tribology).[33] When corrosion processes occur in combination with tribological processes, the resulting effect is known as tribocorrosion; and when tribocorrosion takes place in a biological system it is termed biotribocorrosion.[28,33-35] While it was previously speculated that, after mechanical or electrochemical attacks, biomedical titanium implants can readily be repassivated by a layer of titanium dioxide on their surface, thus preventing further corrosion and dissolution, a new electrochemical peri-implant inflammation model has provided further insights into the behaviors of titanium implants in biological systems. Berbel et al[5] exposed titanium implant surfaces to peri-implant inflammatory conditions and showed, for the first time, that the limited access to oxygen in the peri-implant defect environment limits the ability of the titanium implant surface to be repassivated over time and accordingly reduces the resistance of implants to corrosion. These results support the plausibility of dissolution of titanium from the implant surface during function and inflammatory challenges.

Thus, ions/particles can be released from dental implants as a result of different mechanisms: friction against the bone upon implant placement[36]; wear as a result of micro-movements between contacting surfaces at implant connections[37]; and wear generated by debridement of implants at maintenance visits.[38] In addition, micro-movements at the implant-bone tissue interface can stimulate the release of ions/particles into the biological milieu.[33] These wear mechanisms can be combined with electrochemical processes through the interaction with body fluids (corrosion).[39,40] Moreover, the release of ions/particles can be caused by the corrosive effect of therapeutic substances, such as bleaching agents or fluorides.[41,42] It has also been suggested that long-standing accumulation of oral microbial biofilm on implant surfaces combined with mechanical strain may cause titanium implant surfaces to deteriorate.[43-45]

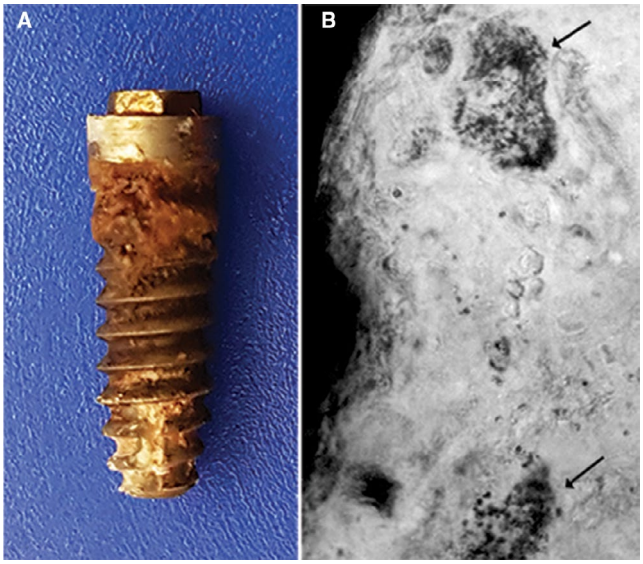


**FIGURE 2** A, Failed human dental implant showing tissue in contact with the metal surface. B, Macrophages close to the surface of the implant (indicated by arrows). Observe the presence of metallic particles in their cytoplasm. Ground section; original magnification ×1000 [Colour figure can be viewed at wileyonlinelibrary.com]

In situ deterioration of a metallic implant alters its structural integrity, and the ions/particles released as a result can trigger a number of biological effects.[46,47] Particularly in the field of dentistry, the possible onset of peri-implantitis associated with the presence of metallic particles, or their interaction or synergistic effect with periodontal pathogens, is a current issue of debate. The corrosion/tribocorrosion phenomena at the metal-tissue interface are particularly important to the clinical course of dental implants. Corrosion/tribocorrosion is one of the possible causes of implant failure after initial success and could result in the loss of close contact between the bone tissue and the implant (ie, loss of osseointegration). In this regard, histopathological examination of peri-implant tissues contributes valuable information to implantology.[30] The study of corrosion/tribocorrosion requires an interdisciplinary approach involving chemists, biologists, physicists, engineers, metallurgists, and specialists in biomedicine. The Biomaterials Laboratory of the Department of Oral Pathology of the School of Dentistry of the University of Buenos Aires has been conducting research on corrosion/tribocorrosion, with the aims of evaluating local tissue response in the peri-implant microenvironment and the systemic effects and possible consequences of corrosion/tribocorrosion, focusing mainly on dental implants.

Several studies have reported the presence of titanium particles in peri-implant tissues.[2,35,48,49] The results on human samples and data obtained using experimental murine models show that any titanium surface can undergo corrosion/tribocorrosion processes and release ions/particles into the local and systemic biological milieu.[46,47] Studies on the local effect of corrosion/tribocorrosion have shown the presence of macrophages loaded with metal-like particles in peri-implant soft tissues of failed human dental implants

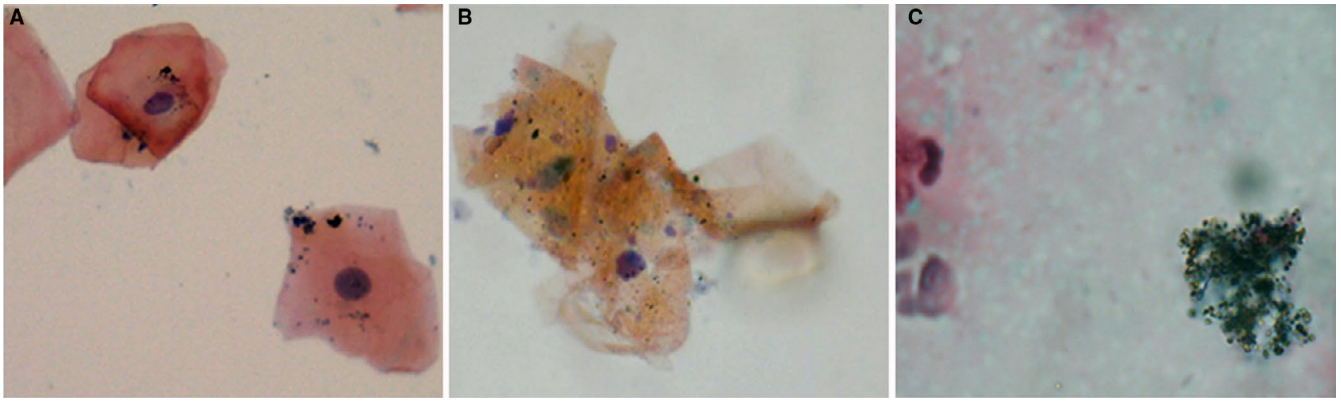


**FIGURE 3** Cytologic smears of peri-implant mucosa from a patient without peri-implantitis. Particles can be seen inside epithelial cells (A and B) and outside cells (C). Papanicolau stain; original magnification ×400 [Colour figure can be viewed at wileyonlinelibrary.com]

(Figure 2). Microchemical investigation of the metallic particles inside macrophages, using energy dispersive X-ray analysis, confirmed the presence of titanium. It is noteworthy that a greater number of macrophages loaded with particles was observed in the vicinity of the metal surface than at more distant sites.[40]The reduced pH, in the electrolytic milieu, as a result of local inflammatory processes would seem to stimulate corrosion.[29,50] It remains controversial whether an inflammatory process, associated with the decrease in pH, generates corrosion or whether corrosion triggers an inflammatory reaction. Regardless, the presence of macrophages loaded with titanium particles is considered a bioindicator of corrosion/tribocorrosion processes.

We also performed an experimental study in which the biological effect of pitting corrosion, a type of localized corrosion, on the peri-implant environment was analyzed.[51] Pitting corrosion produces local attack, especially on isolated spots of the passivated metal surface, which propagates into the metal. The results of our histological studies showed scarce osseointegration at the bone-implant interface in such areas. The decreased percentage of osseointegration in the areas corresponding to the pits may be associated with a change in the chemical composition and/or structure (eg, crystallography) of the oxide on the pitted surface. It is important to point out that the presence of particulate corrosion and wear products in the tissue surrounding the implant may ultimately result in a cascade of events leading to periprosthetic bone loss.[39,52] Microchemical investigation of corrosion products in the peri-implant milieu, using energy dispersive X-ray analysis, revealed the presence of titanium. It is noteworthy that craters, pits, surface cracks, and depressions may appear during the preparation of the sheets that will be used to manufacture miniplates,[53] and could be potential sites for the initiation of corrosion. The results of our histological studies show the presence of corrosion products in peri-implant tissues, both outside cells in the intercellular spaces and/or phagocytosed in macrophages. In various cases, the products of corrosion were found close to blood vessels. The observation of metal particles located intracellularly or in association with vessels may indicate a biological response aimed at eliminating the foreign material.[54]

In another study, we evaluated tissue responses to implants by analyzing human oral mucosa in contact with submerged titanium implants, using biopsies of the supra-implant oral mucosa adjacent to the implant cover screw.[30] We observed particles of different sizes in the intercellular spaces and inside macrophages in the connective tissue. It is of note that smaller particles were located in the superficial layers of the epithelium. Microchemical investigation using energy dispersive X-ray analysis revealed the presence of titanium in the particles. Immunohistochemical staining with antibodies to CD68 and CD45RO was positive, confirming the presence of macrophages and T lymphocytes, respectively, associated with the metal particles. In agreement with other reports,[55,56] the T-lymphocyte infiltrate would seem to suggest the presence of an immune response mediated by cells.

Another study design developed by our research team involved assessing the presence of corrosion/tribocorrosion-related metallic particles in cells exfoliated from peri-implant oral mucosa around titanium dental implants (Figure 3). The study sample included implant-carrying patients with and without peri-implantitis. We found metal particles both outside and inside epithelial cells and macrophages. The concentration of titanium, as determined by inductively coupled plasma-mass spectrophotometry, was higher in the peri-implantitis group than in the group without peri-implantitis; no traces of titanium were observed in control patients. Our results confirm, on the one hand, that an inflammatory response and subsequent decrease in pH trigger corrosion and the release of ions/particles into the biological milieu. On the other hand, they also show that, regardless of an inflammatory response, ions/particles are released from the surface of the implant into the biological milieu. Thus, we have proposed the use of peri-implant exfoliative cytology as a simple and useful method to assess corrosion/tribocorrosion of titanium dental implants.[48] Such findings suggest that the release of titanium ions/particles into the tissues may play a role in the pathogenesis of peri-implant diseases.[43]

We have also reported the occurrence of reactive lesions (inflammatory angio-hyperplastic granuloma and peripheral giant cell granuloma) in peri-implant mucosa in close contact with dental implants, in which the presence of metallic particles was detected

histologically. Given the controversial origin of reactive lesions, and in view of our results, we suggest that the presence of metallic particles in the tissue studied may potentially contribute as an adjuvant etiological factor for the development of these lesions.[57] In line with the aforementioned study, we analyzed a series of cases of infrequent lesions, located close to a titanium dental implant, which were retrieved from the archives of the Surgical Pathology Laboratory of the School of Dentistry, University of Buenos Aires (1990-2015). The lesions covered a broad spectrum of pathologies, ranging from diseases of inflammatory origin to neoplastic lesions. The presence of metallic particles was observed in 24 (48%) cases, all of which showed inflammation. Microchemical investigation of the particles using energy dispersive X-ray analysis revealed the presence of aluminium, silicon, manganese, titanium, iron, nickel, tungsten, cobalt, zirconium, vanadium, chromium, and barium. Again, the particles may potentially contribute as an adjuvant etiological factor for the development of lesions.

Based on the aforementioned observations, the occurrence of corrosion/tribocorrosion phenomena at the metal-tissue interface is of paramount importance to the clinical course of dental implants because such phenomena could be a possible cause of mid-term implant failure.[46] Moreover, the issue of corrosion/tribocorrosion is not only a local problem as particles resulting from this process are able to migrate to distant sites. Hence, the local effect of corrosion/tribocorrosion and the subsequent release of ions/particles into the peri-implant biological environment may compromise other biological compartments. In this regard, our studies in experimental animal models demonstrate systemic deposition of titanium micro- and nanoparticles and the presence of a tissue response to these particle deposits in target organs.[58-63]

## 5 | FINDINGS OF PARTICLES IN THE TISSUES SURROUNDING CERAMIC DENTAL IMPLANTS

With the aim of limiting the potential adverse effects on tissues of ions/particles resulting from metallic implants, it is paramount to develop implant surface treatments that effectively prevent biotribocorrosion-related problems, or to develop new nonmetallic materials (ie, metal-free dental implants). Zirconia dental implants are a therapeutic alternative to titanium metallic implants.[64,65] The use of zirconia would rule out the possibility of ion/particle release into the biological milieu as a result of tribocorrosion. In vivo and in vitro studies on the biological properties of zirconia show that zirconia implants stimulate only small amounts of inflammatory infiltrate, have low affinity for accumulation of bacterial plaque, demonstrate good biocompatibility with, and integration into, soft tissues,[65,66] and exhibit effective osseointegration.[67] In addition, zirconia implants are white and opaque, thus improving esthetics, especially when placed in patients with a thin gingival biotype.[66] Zirconia has also shown promising physical and mechanical properties, such as low thermal conductivity, high resistance to flexion (900-1200 MPa), adequate fracture resistance, as well as resistance to wear and corrosion.[66] Nevertheless, despite the excellent properties of this biomaterial, further basic and clinical studies must be conducted to evaluate long-term outcomes and technical and biological complications associated with zirconia implants.

In a previous descriptive pilot study we evaluated, using histopathology, the tissue response of human oral mucosa adjacent to zirconia dental implants.[68] Olmedo et al. analyzed 43 samples of supra-implant oral mucosa, obtained by biopsy of tissue adjacent to 2-piece zirconia dental implants (Zeramex® [T-$ZrO_2$ 76%, $Al_2O_3$ 20%, $Y_2O_3$ 4%]; Dentalpoint AG, Switzerland), 3-4 months post-implant placement. All mucosal samples showed epithelial hyperplasia and dense fibrosis with chronic inflammatory infiltrate and without multinucleated giant cells in the connective tissue. In addition, a fine particulate material, deposited evenly throughout the epithelial and connective tissues, was observed. Investigation of the chemical composition of the observed particulate material, using energy dispersive X-ray analysis, showed the presence of aluminum, iron, zirconium, titanium, silica, chromium, nickel, silver, gold, hafnium, carbon, and oxygen.

The presence of metals, particularly aluminum and zirconium, in the tissues adjacent to zirconia dental implants shows the need for further studies to evaluate the effect of these metals on peri-implant tissues and their influence on the clinical course of metal-free zirconia dental implants. Thus, future actions include performing histological studies in a large number of tissue samples to evaluate the chemical composition of the metallic particles detected in peri-implant tissues and to determine their origin, and evaluating baseline concentrations of metals in healthy control samples of oral mucosa.

### 5.1 | Titanium particles elicit potent pro-inflammatory immune responses

Ions/particles released as a result of degradation of the dental implant system can act as foreign bodies to the immune system, thus stimulating activation of a number of chemical mediators associated with bone resorption and peri-implant diseases.[35,69] Petterson et al[25] suggest that stimulation of the pro-inflammatory response is caused by titanium-based particles and not by the ionic form of titanium. Thus, titanium-based particles could act as additional stimuli for a pro-inflammatory reaction.[25] Macrophages are cells that respond to in vivo implantation of biomaterials, with the macrophage reponse depending, among other variables, on the size and structure of the material.[70] Microparticles and nanoparticles could differ in their action on cells. Nanoparticles have been described as more biologically reactive and more potentially harmful than microparticles because of their greater surface-to-volume ratio. Nanoparticles can aggregate in a microparticle size range and change their recognition by the host, hence decreasing the inflammatory response.[12] It is important to point out that in addition to particle shape, other variables, such as concentration

and composition, chemical reactivity, and host response, can affect the local immune response.[34]

Histological examination of, of peri-implant tissue in contact with failed human dental implants showed macrophages loaded with titanium particles, which suggests the potential of these cells as bioindicators of corrosion/tribocorrosion processes.[40] It is also known that the ions/particles ingested by macrophages stimulate the release of cytokines that contribute to bone resorption by activating osteoclasts. In addition to increasing bone reabsorption, the particles can suppress osteoblast function, reducing bone formation and contributing to osteolysis.[39,71,72] The above mechanisms may have been the cause of implant failure in the cases included in our study.

Moreover, in addition to epithelial cells, we also observed macrophages loaded with titanium particles in exfoliative cytology samples of peri-titanium implant mucosa.[48] In our study on supra-implant oral mucosa adjacent to implant cover screws, positive staining for antibodies to CD68+ and CD45RO+ confirmed the presence of macrophages and T lymphocytes, respectively, which were associated with the particles. In agreement with other reports,[53,55] the T-lymphocyte infiltrate would seem to suggest the presence of an immune response mediated by cells. Thus, hypersensitivity or intolerance to titanium as an implant material in oral and maxillofacial surgery probably occurs more commonly than has been reported in the literature.[56] This reaction to titanium could be responsible for unexplained successive failures of dental implants in some patients.[55] There are reports in the literature of cases in which titanium allergy/intolerance mainly appeared as the fundamental cause of urticaria, eczema, edema, and redness and pruritus of the skin or mucosa, localized, at distant sites, or generalized.[73] However, the clinical relevance of allergic/intolerance reactions in patients with titanium dental implants remains a matter of debate.[74]

The potential toxicity and biological risks associated with ions/particles originating from biotribocorrosion are critical issues in patients with a prosthesis because these implants remain in the body for a long period of time. In this regard, management and control of biotribocorrosion of biomedical implants is an important issue at biological, sanitary, metallurgic, economic, and social levels.[46,49]

Our studies suggest that associations exist among corrosion/tribocorrosion, the presence of titanium particles, and biological complications. However, further research is needed to better understand the role of ion/particle release in the pathogenesis of peri-implant diseases.

## 6 | TITANIUM DISSOLUTION PRODUCTS ARE MICROBIOME COMMUNITY ACTIVISTS THAT SHAPE MICROBIOME STRUCTURE AND DIVERSITY

Early investigations of peri-implant biofilms using targeted approaches focused on known periodontal pathogens, such as *Porphyromonas gingivalis* and *Treponema denticola*, and eventually detected them in peri-implant plaque. The majority of previous microbial investigations of peri-implantitis have a priori considered the similarities between periodontitis and peri-implantitis. Red complex species confirmation bias led to the direct transfer of knowledge for treatment of periodontitis (including antimicrobials, systemic antibiotics, and surface scaling) to treatment of peri-implantitis. A 2012 systematic review concludes that the relapse rate of antimicrobial treatments for peri-implantitis, at 1-year post-treatment, may be as high as 100%,[3] which is alarming.

The first study to highlight the distinct signature of the peri-implant microbiome compared with the periodontal microbiome performed an unbiased investigation of 40 subjects with periodontitis, peri-implantitis, periodontal health, and peri-implant health.[26] Using 16S pyrosequencing it was found that the peri-implant microbiome composition was largely composed of oral taxa previously unsuspected to be related to gingival inflammation. While these differences offered a plausible explanation for the differential response to treatment between implants and teeth, the cause of these differences remained unknown until the 2017 study by Daubert et al.[75] This study capitalized on a novel method for the parallel investigation of microbiome composition and titanium concentration in peri-implant plaque and unveiled a strong role of titanium particles in shaping the peri-implant microbiome. Titanium concentrations in plaque were inversely correlated with species richness (see Figure 1). Furthermore, variations were found in the structure of the microbiome community, not only between disease and health, but also when high titanium concentrations were present. More specifically, microbiome beta diversity in healthy sites with high titanium concentrations was very similar to that of diseased microbiotas. In a more granular analysis, the presence of titanium enriched for selected taxa, such as *Veillonella* spp (significant positive correlation of $\rho = .062$ [$P < .05$]). Importantly, *Veillonella* spp are an example of candidate peri-implant pathogens that fit the proposed model of infection: they have a potent lipopolysaccharide that can activate rapid bone loss, they are resistant to penicillins and metals (titanium), they can coaggregate on titanium substrates with streptococci, and finally their biofilms have high antibiotic resistance. These findings support a strong role of titanium dissolution products in peri-implantitis, which may indirectly result in a shift of the peri-implant microbiome toward dysbiosis. In corroboration, recent studies focusing on potential causative factors of peri-implantitis have consistently pointed to titanium particles as being associated with peri-implant inflammation.[33,35,76,77]

## 7 | CONCLUDING REMARKS

- No metal or alloy is completely inert in vivo. In situ degradation of a metallic implant is an unwanted, but factual, event.
- Metal corrosion/tribocorrosion affects peri-implant biofilms and may directly (ie, through immune modulation) or indirectly (ie,

through microbiome perturbation) lead to peri-implant inflammation and implant failure.

- Corrosion/tribocorrosion is also a systemic problem because particles could migrate systemically in serum and blood cells, and deposit in target organs.
- While zirconia implants are a new alternative to titanium dental implants, detection of metals, particularly aluminum and zirconium, in tissues shows the need for further studies to determine the origin of the metal particles and to evaluate the effect of these metals on peri-implant tissues and their influence on the clinical course of zirconia dental implants.
- It is important to highlight that the effects of corrosion/tribocorrosion are not always a determining factor of the course of an implant. The possible biological effects do not occur in all implant-carrying patients because biological responses differ from one individual to another.
- The de novo investigation of peri-implant biofilms with consideration to implant-related environmental factors is necessary and has strong potential to lead to efficacious, implant-driven peri-implantitis therapies that are critical to limit the health burden resulting from implant inflammatory disease.

## ACKNOWLEDGMENTS

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