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REVIEW ARTICLE

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The role of foreign body response in peri-implantitis: What is the evidence?

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1 | INTRODUCTION

The 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions identified the plaque biofilm as the key etiological factor for the development of peri-implant mucositis and peri-implantitis.[1] The cause-and-effect relationship between the accumulation of bacterial biofilms around titanium dental implants and the development of inflammation (peri-implant mucositis) is well established in humans.[2–5] Given that peri-implantitis is an irreversible disease, it is impossible from an ethical perspective to obtain direct evidence for a causative relationship between plaque and peri-implantitis. However, observational studies show that patients exhibiting poor plaque control and not attending regular maintenance therapy are at a higher risk of developing peri-implantitis.[6] Furthermore, the treatment of peri-implantitis with anti-infective strategies has been shown to be successful in decreasing soft tissue inflammation and suppressing disease progression.[7] Therefore, the available evidence appears to strongly support the current paradigm that plaque is the primary etiological agent for peri-implant mucositis and that in susceptible patients it will progress to peri-implantitis, with inflammation being the key biological mechanism in the pathogenesis of both diseases. It is also recognized, however, that risk factors and indicators associated with the establishment and progression of peri-implantitis are not fully understood. Indeed, it has been acknowledged that non–plaque-related factors, such as peri-implant keratinized mucosa, occlusal overload, titanium particles, bone compression necrosis, overheating, micromotion, and biocorrosion, may play a role in the etiology of peri-implantitis, but their influence is unknown.[1]

In the past decade, the potential role of non–plaque-related factors in the pathogenesis of progressive peri-implant bone loss has been brought to prominence in several reviews.[8–15] In particular, the role of the "foreign body reaction" towards the implanted material has been proposed as an important contributor to the pathogenesis of peri-implant bone loss.[12] Therefore, this review will explore the evidence for a role of "foreign body reaction" in peri-implantitis by examining the influence that implant-related factors may have in initiating or exacerbating the progressive crestal bone loss that is characteristic of peri-implantitis. The focus will be on the implant componentry that resides within soft and hard tissues (implant fixture, abutment) but will not address iatrogenic factors that have been shown to cause peri-implant tissue complications, such as retained cement, incorrect implant positioning, inappropriate surgical technique (overheating, excessive compression), incomplete abutment or restoration seating, and occlusal trauma. In particular, three issues will be addressed:

1. Does osseointegration represent a return to "homeostasis" or a "chronic inflammatory" state akin to an unresolved "foreign body reaction"?
2. Does a foreign body reaction to an osseointegrated implant have a role in crestal bone loss characteristic of peri-implantitis?
3. Following a period of function, can materials released from the implant componentry that resides within soft and hard tissues (implant fixture, abutment) initiate or exacerbate peri-implantitis?

2 | FOREIGN BODY REACTION AND OSSEOINTEGRATION

Contemporary understanding of the host response to biomaterial implantation acknowledges that there is no such thing as a totally

inert biomaterial and that all implants will elicit a host response.[16] However, it is also clear that certain materials result in a "foreign body reaction" characterized by chronic inflammatory response and fibrous encapsulation, whereas others are seamlessly incorporated into the host tissue ("restitutio ad integrum"), thus achieving homeostasis. These are likely to represent two extremes of a continuum of potential responses, with contemporary biomaterial science and tissue engineering focused on strategies to attenuate the inflammatory response and encourage biomaterial integration.[17,18] An important question is where titanium implant osseointegration fits within this spectrum of potential outcomes; that is, whether it represents a return to "homeostasis" or whether it is a "foreign body response" characterized by a chronic inflammatory state.

2.1 | The foreign body response—What is it?

The term "foreign body response" has been frequently used in the biomaterial science literature, most commonly in the context of an inappropriate response to the insertion of a material. Although there is no universally accepted definition for a foreign body response, a commonly accepted description is a "reaction composed of macrophages and foreign body giant cells (that) is the end-stage response of the inflammatory and wound healing responses following implantation of a medical device, prosthesis, or biomaterial."[8] Essentially, the outcome of foreign body response historically has been regarded as an adverse end-stage outcome, with either complete rejection of the biomaterial in the short term or initial fibrous encapsulation and failure of the biomaterial in the long term. The adverse foreign body response–associated biomaterial failure is often characterized histologically by the presence of foreign body/multinucleated giant cells surrounding the biomaterial.

Detailed discussion of the various theories about the pathophysiology of foreign body response is beyond the scope of this review, and there are several published reviews on this topic.[19–22] In summary, an adverse foreign body response to an inserted biomaterial is understood to comprise five stages: (a) protein adsorption, (b) acute inflammation, (c) chronic inflammation, (d) foreign body giant cell formation, and (e) fibrosis/fibrous capsule formation.[16,19] An important consideration is that the early phases (protein adsorption and acute inflammation) will occur irrespective of any biomaterial that is surgically inserted into a host tissue. What happens thereafter is dependent on various factors, including the nature of the surgical wound, the characteristics of the biomaterial, and how the recipient tissue responds to it. Therefore, the early inflammatory wound-healing response to the insertion of a biomaterial is critical for the downstream events that lead to implant integration or encapsulation (foreign body response).

In the context of dental implantology, the traditional understanding of osseointegration is that, following the insertion of the implant, the initial inflammatory reaction will in most cases resolve, which returns the surrounding soft and hard tissues to a state of homeostasis. This is characterized by the formation of new alveolar bone in direct contact with the implant surface. A continuation of the foreign body response, whereby tissue does not return to homeostasis, results in the rejection of the implant, which is an infrequent finding associated with early implant loss. The latter is typified by a persistent inflammatory state that leads to soft-tissue encapsulation of the implant and the presence of foreign body/multinucleated giant cells, which is characteristic of the traditionally accepted "foreign body response" concept. Therefore, an understanding of the key inflammatory mechanisms involved in the wound healing process is crucial for understanding the nature of the implant-host relationship following osseointegration.

2.2 | Inflammation and osseointegration

Inflammation is a fundamental step during wound healing. Since implant placement involves surgical trauma of the recipient site, the initial wound healing leading to osseointegration is intimately involved with the process of peri-implant osseous healing, which is like events during bone fracture repair (Figure 1).[23] This process is relatively complex and can be broadly characterized into four overlapping phases: hemostasis, inflammation, proliferation/matrix formation, and remodeling.[24] An inflammatory reaction is elicited rapidly following the surgical insertion of an implant, after hemostasis is achieved and protein is adsorbed onto the implant surface. A prolonged inflammatory response can potentially trigger a "foreign body response" that leads to a lack of integration of dental implants, whereas a timely resolution of the inflammation leads to repair via the formation of bone at the implant interface. Therefore, the nature of the initial inflammatory response is considered critical for the downstream events leading to osseointegration.

Macrophages have long been considered the key regulators of the early inflammatory response during wound healing following the insertion of a biomaterial. Macrophages are also important in the context of foreign body response, as they are the precursors to the multinucleated giant cells that are characteristic of this condition. Crucially, depending on the phenotype of the macrophages at the wound site, their secretory profile, and hence their function throughout the course of the inflammatory phase, will differ, therefore influencing downstream events in wound healing. Briefly, macrophages can be broadly divided into two subsets.[25] M1 macrophages are predominantly found in the early stages of the inflammatory phase and express high levels of proinflammatory cytokines and reactive nitrogen and oxygen intermediates. By contrast, M2 macrophages are mainly found at the conclusion at the inflammatory phase, secreting low levels of proinflammatory cytokines and high levels of anti-inflammatory cytokines that promote wound healing and regeneration.[26] It is now recognized that M1 and M2 phenotypes represent two extremes of the macrophage phenotype that have been characterized *in vitro*, whereas the *in vivo* situation is far more complex, with a spectrum of phenotypes present that have not been fully characterized.[27,28] Furthermore, it is also clear that macrophages are not the only cells that are

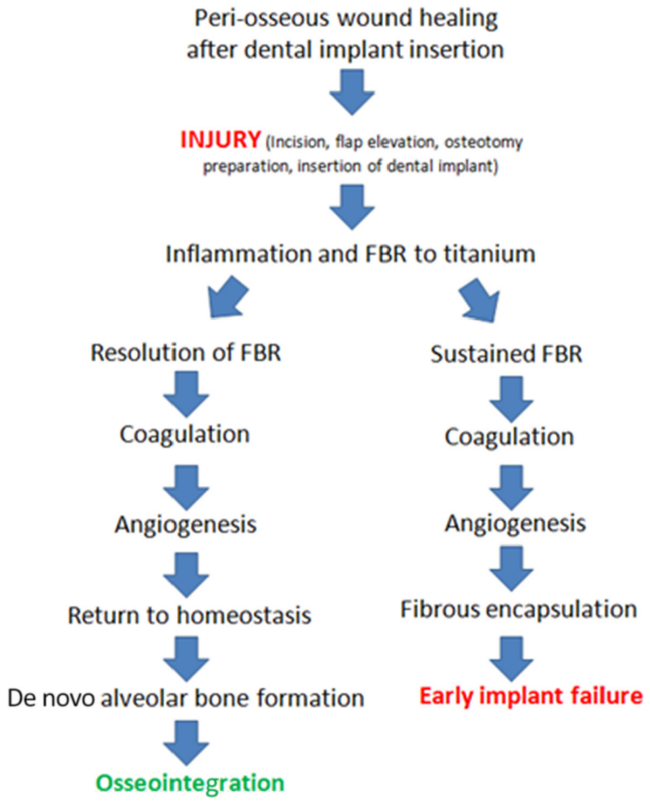

FIGURE 1 Current understanding of the possible sequelae of dental implant placement into alveolar bone. During osseointegration, the initial inflammatory response is followed by timely resolution and pro-reparative processes leading to osseointegration and bone formation at the implant interface. The inability to resolve the initial inflammatory response leads to a chronic inflammatory state and fibrous encapsulation of the implant, which is characteristic of a foreign body response that leads to early implant failure. FBR: foreign body response

important in regulating the wound healing process, with neutrophils, lymphocytes, and other cells of the immune system playing a role.[29] Nevertheless, in the context of this review, it is important to appreciate the transition from an M1- to an M2-type response as important in establishing osseointegration, whereas a persistent M1-type response can lead to impaired healing leading to a "foreign body response."

2.3 | Osseointegration—Return to "homeostasis" or a "chronic inflammation" state?

Although "osseointegration" has been traditionally considered to represent a physiological state whereby the titanium implant is integrated into the host, it has more recently been suggested in a series of reviews that it should instead be viewed as a "foreign body response" representing a "chronic inflammatory" state.[8,11,30] However, considerable support remains for the conventional notion that osseointegration is a return to "homeostasis" rather than a "foreign body reaction/chronic inflammatory state."[31] To fully appreciate this controversy, the available evidence regarding the healing response leading to osseointegration needs to be considered.

The conventional understanding of osseointegration as a return to homeostasis is based on the original observations showing a direct bone-implant contact between titanium implants and the recipient alveolar bone.[32,33] Thereafter, the temporal events leading to inflammation have been extensively studied and show that the early inflammatory response leads to a resolution of an early inflammatory state to ultimately result in direct apposition of bone on the implant surface.[34] Complementary histological and molecular assessments of the temporal wound-healing events leading to osseointegration in humans show that the initial inflammatory response is subsequently attenuated and replaced with anabolic biological processes, such as osteogenesis and angiogenesis, which eventually return the tissue to homeostasis and functionality.[35,36] Indeed, an acceleration of the transition between a proinflammatory M1 to a reparative M2 inflammatory response is considered the major mechanism for enhanced osseointegration associated with the latest generation of titanium implant surfaces.[35-44]

More recently, the concept that dental implant osseointegration represents a return to "homeostasis" has been challenged by a theory that an osseointegrated implant constitutes a foreign body response characterized by a mild "chronic inflammatory state."[11] This is considered to represent a "foreign body equilibrium," whereby the implant is "encapsulated" by bone.[11] The primary evidence provided in these narrative reviews to support this theory is the presence of multinucleated giant cells, demonstrated adjacent to an osseointegrated implant in one slide, and proposed to be "foreign body giant cells." Interestingly, the presence of multinucleated giant cells has also been more conclusively demonstrated at the surface of osseointegrated dental implants by another group, albeit with a different interpretation of their presence.[45] In that study, multinucleated giant cells were shown to be associated with the bone-implant interface of osseointegrated titanium and zirconia dental implants, without the persistence of any chronic inflammation and no impaired/compromised bone formation.

The question of whether osseointegration can be considered as a return to homeostasis or as a chronic inflammatory state needs to be considered in the context of our understanding that any biomaterial that is surgically inserted into a host will elicit a response, and hence cannot be considered absolutely "inert." This then brings up the issue of whether the presence of a titanium implant changes the course of healing within a recipient osteotomy. This has been addressed in several studies, and it has been demonstrated that there are molecular mechanisms that are altered upon the insertion of an implant; but these are generally considered to be pro-osteogenic processes important for bone formation and maintenance, rather than anything that can be associated with a foreign body response or a chronic inflammatory state.[46,47] Indeed, recent studies by the same group that proposed the "foreign body equilibrium theory" have explored the effect of the implant presence within the healing osteotomy, showing increased bone formation at the implant-bone interface (compared with pristine osteotomy healing) and an

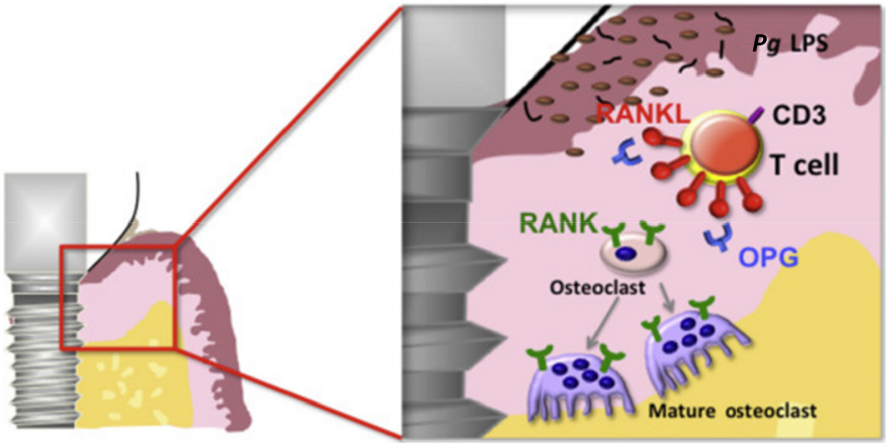

FIGURE 2 Diagrammatic representation of the plaque-associated pathogenic mechanism for crestal bone loss. In this mechanism, an inflammatory response to biological mediators released from plaque induces an inflammatory response from the host that results in the activation of osteoclasts responsible for crestal bone loss. *Pg* LPS: *Porphyromonas gingivalis* lipopolysaccharide; OPG: osteoprotegerin; RANK: receptor activator of nuclear factor-κB; RANKL: receptor activator of nuclear factor-κB ligand. Diagram adapted from ref. [51]

enhancement of the M2 macrophage response in implant recipient sites compared with empty osteotomies.[48] These findings are consistent with the notion that titanium is a highly biocompatible and osteoconductive biomaterial, and hence it is not surprising that there is enhanced bone formation at the interface of the implant. The exceptional biocompatibility of titanium was further demonstrated by the same group in a study comparing the healing outcomes of titanium compared with copper and polyether ether ketone implants.[49] The titanium implants were shown to achieve a transition to an M2 reparative healing phenotype at a faster rate than the other implants. These findings are consistent with the notion that osseointegration of a titanium implant results in a return to "homeostasis," providing no evidence of a persistent chronic inflammatory state.

Collectively, the available evidence supports the notion that all biomaterials inserted in the body will elicit an inflammatory response and that resolution of inflammation is important to return the host tissue to functionality and homeostasis. Importantly, titanium implants can facilitate the resolution of the initial immuno-inflammatory response to favor a healing and reparative response that facilitates the formation of bone directly on its surface (Figure 1). By contrast, a nonresolving foreign body response will lead to fibrous encapsulation and implant failure, which is an infrequent finding associated with early bone loss (Figure 1). Notwithstanding the need to further elucidate the biological mechanism associated with the maintenance of osseointegration, there is currently no evidence that a chronic inflammatory state is associated with a healthy, osseointegrated dental implant.

It is important, however, to note that the apparently opposing views on implant osseointegration share many common aspects. Both acknowledge that no biomaterial is truly "inert" and that the inflammatory response plays a key role in determining the outcome of a host's response to titanium implant placement. Both recognize the classic "foreign body response" as a soft-tissue encapsulation and a failure of osseointegration. Where they differ is on whether osseointegration represents a "mild chronic inflammatory state" or a return to "homeostasis." This is a somewhat academic argument in the context of osseointegration, but it has more practical implications in terms of understanding, and more importantly treating, peri-implantitis. A key consideration is whether the multinucleated giant cells present at the surface of an osseointegrated implant are involved in the etiology of peri-implant bone loss characteristic of what has been classified as peri-implantitis.

3 | FOREIGN BODY REACTION AND PERI-IMPLANTITIS

In the widely accepted concept of osseointegaration being a return of homeostasis, dental plaque plays a central role in initiating and progressing crestal bone loss (Figure 2), and hence forms the primary target for treatment. This approach is supported by studies that show a key role for plaque in the etiology of peri-implant mucositis and periodontitis. For peri-implant mucositis, a direct cause-and-effect relationship between biofilm and development of inflammatory responses has been demonstrated in humans.[2,3,5] It has also been demonstrated that there is a significant dose-dependent association between plaque scores and mucositis[50] and that lack of compliance is associated with higher incidence of mucositis.[6] The key role of dental plaque in peri-implantitis is supported by studies that show patients exhibiting poor plaque control and not attending regular maintenance therapy are at a higher risk of developing peri-implantitis.[6] Further, anti-infective treatment strategies are successful in decreasing soft-tissue inflammation and in suppressing disease progression.[7]

Proponents of the "foreign body equilibrium/bone encapsulation" theory, on the other hand, consider a variety of external factors—of which dental plaque may be one factor but is not considered to be the primary one—exacerbate a latent inflammatory response, mediated by resident foreign body giant cells (Figure 3). This clearly

has important implications for treatment, since the focus on managing dental plaque is far greater in the conventional compared to this alternative theory. Notably, there does not appear to be a clear strategy for the management of peri-implant mucositis and peri-implantitis in the context of the foreign body equilibrium concept, since the proposed etiological mechanism may be one of a variety of poorly defined and understood "external factors." Indeed, it has been proposed that the "underlying chronic inflammation (FBE) observed around oral implants leads to the conclusion that mucositis need not automatically be coupled to disease," and that "marginal bone loss after the implants first year in situ need not be automatically coupled to disease."[30] Clearly, since the foreign body equilibrium concept considers inflammation and bone loss to be a physiological rather than a "pathologic" phenomenon, this downplays the role of dental plaque in peri-implantitis.[14,15] This has important implications on how we view and subsequently treat inflammation and bone loss around dental implants.

A central premise to the foreign body equilibrium theory for peri-implant bone loss is that the presence of "multinucleated" cells around osseointegrated dental implants—ambiguously and universally classified as "foreign body giant cells"[12]—constitutes a mild chronic inflammatory state. Subsequent disruption of this "equilibrium" leads to breakdown of osseointegration and ultimately crestal bone loss. Therefore, an understanding of the potential role of multinucleated cells associated with healthy, osseointegrated implants is necessary to appreciate their potential role in peri-implantitis.

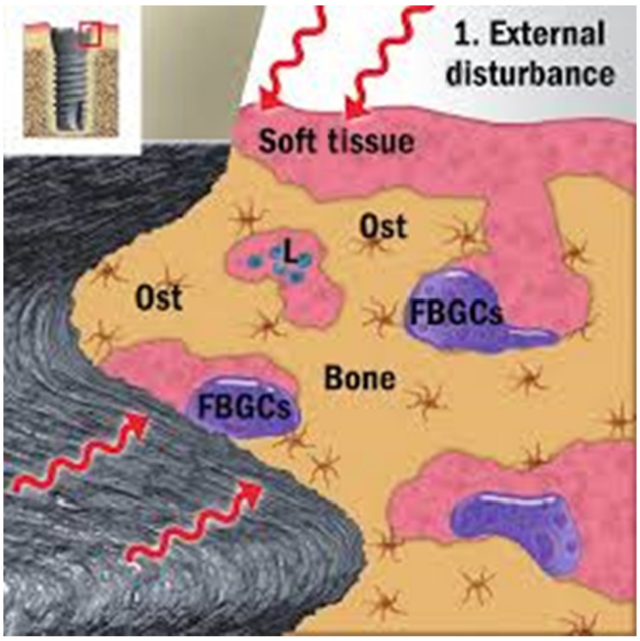

FIGURE 3 Diagrammatic representation of the "foreign body equilibrium" disturbance theory of peri-implant bone loss. In this concept, the osseointegrated implant is considered "encapsulated in bone," thus representing a chronic inflammatory state characterized by the presence of "foreign body giant cells" (FBGCs). In response to a variety of external stimuli, these foreign body giant cells are activated and are responsible for the peri-implant bone loss. L: lymphocyte; Ost: osteocyte. (Diagram adapted from ref. [32])

There is no doubt that multinucleated giant cells do appear around biomaterials, and several recently published reviews have explored their role in wound healing and implant rejection (foreign body response).[20,22,23] It is clear from the reviews that not all multinucleated giant cells observed histologically are similar, and it has been proposed that they may be serving different purposes (both favorable and unfavorable for integration) in various conditions. It is inappropriate,therefore, simply to brand them as "foreign body giant cells." Indeed, it has been proposed that the multinucleated giant cells could be classified as both proinflammatory M1–multinucleated giant cells (this can be defined as the foreign body giant cells that are associated with foreign body response) and pro-reparative M2–multinucleated giant cells, to mimic the current M1-M2 macrophage phenotype paradigm. Indeed, within biomaterial science, it has been shown that the presence of multinucleated giant cells is frequently observed and can be considered a physiological (rather than "pathological") response to implantation of biomaterials.[24–26,28]

Aside from the mere presence of multinucleated giant cells being considered evidence of an underlying chronic inflammatory state, the other issue with the foreign body equilibrium concept of peri-implant disease is the crestal pattern of bone loss that is characteristic of peri-implantitis. If the resident multinucleated giant cells are indeed responsive to external stimuli and responsible for bone loss during peri-implant disease, then their even distribution along the implant would suggest a uniform rather than a localized (crestal) pattern of bone loss that is observed in peri-implantitis.

Notwithstanding the need for further research in this area, there is currently no evidence in the existing literature to suggest that the presence of multinucleated giant cells on a healthy, osseointegrated dental implant is a risk factor for peri-implantitis. Given there is clear evidence that poor plaque control leads to peri-implantitis and that the targeting of plaque leads to favorable treatment outcomes (albeit not in all cases), the weight of evidence favors the current concept that plaque is the key etiological factor in the development of peri-implantitis, and hence an obvious primary target for therapeutic approaches for managing the disease.

4 | WHAT IS THE ROLE OF THE NON–PLAQUE-RELATED FACTORS IN THE PATHOGENESIS OF PERI-IMPLANTITIS?

Thus far, we have established that there is no evidence to suggest that a foreign body reaction to an osseointegrated implant contributes to the crestal bone loss that is characteristic of peri-implantitis. However, it must be acknowledged that an osseointegrated dental implant is unique compared with most other implanted biomaterials, as it is transmucosal and resides in an oral environment that favors microbial plaque formation. Further, the position of an implant-abutment interface in the vicinity of the bone crest has the potential to influence crestal bone loss due to several anatomical, functional,

iatrogenic and implant related factors. Indeed, it was acknowledged by the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions that the role of several non–plaque-related factors—including peri-implant keratinized mucosa, occlusal overload, titanium particles, bone compression necrosis, overheating, micromotion, and biocorrosion—is not fully understood.[1] Since the focus of this review is on implant-related factors, the possible role of titanium particles and biocorrosion will be explored in greater detail.

4.1 | Titanium particles

It is indisputable that titanium particles have been found in peri-implant tissues. Their potential role in peri-implant inflammation and crestal bone loss has been addressed in a critical narrative review.[13] The release of titanium particles after implant placement into surrounding peri-implant tissue, as well as in lymph nodes and various internal organs, has been documented in animal models.[52–54] In human studies, the presence of metal particles has been reported in macrophages located in peri-implant hard and soft tissue.[55,56] Indeed, metal-like particles have been identified both inside and outside cells in cytologic smears of tissues around both diseased and healthy implants.[57]

In vitro experiments have shown the potential of titanium ions or particles to have toxic or proinflammatory effects.[58,59] Further, the deliberate introduction of titanium particles during osseointegration in a mouse model has been shown to induce M1 macrophage phenotype polarization and associated bone loss.[60] *In vitro* research has also identified factors modulating such effects, such as particle size. Nanoparticles are considered more biologically reactive and more potentially harmful than microparticles because of their greater surface-to-volume ratio.[61,62] However, these observations are not universal, as it has also been shown that microparticles (1-3 μm) induce a greater inflammatory response by neutrophils than nanoparticles do.[63] The effect of particle size is further complicated by the fact that nanoparticles can aggregate in a microparticle size range and change their recognition by the host, hence modulating the inflammatory response. Aside from particle size, it has been shown that lower pH and higher lipopolysaccharide concentration accelerate titanium corrosion *in vitro*.[64]

The source of titanium particles is not fully understood and remains controversial. It has been shown that titanium particles may be disseminated from local to distant sites via the bloodstream,[55,56] but it is also possible that they may be introduced from nonoral sources.[61] Indeed, it has been shown that titanium is present in the peri-implant mucosa from individuals with or without titanium implants.[57] The presence of titanium particles in patients without titanium implants can be attributed to the widespread use of titanium dioxide as micro- or nanoparticles in foods, toothpastes, cosmetics, sunscreens, and medicine pills.[65]

One obvious source of release of titanium particles is the implant-abutment connection, and there is substantial evidence of the formation of wear debris due to mechanical stress at the implant-abutment interface from *in vitro* studies.[66–68] Further, in a cadaver study, titanium particles in size between 0.5 and 40 μm were clearly evident in jawbone tissues associated with osseointegrated implants, although, notably, these were not affected by disease. The titanium count decreased as the distance away from the implant increased.[69] Collectively, these studies suggest that titanium particles released from the micromovement between the abutment and the implant are certainly possible under force transmission, although they are not present in all cases.[70]

Samples from multiple oral sources have been assessed for the presence of implant particles, including mucosa overlying titanium cover screws during submerged healing,[71] mucosa from both peri-implantitis lesions[72–74] and implants without clinical signs of pathology,[58] and gingiva from healthy teeth.[75] In a recent histopathological analysis of biopsies from both peri-implantitis and periodontitis sites, titanium particles were identified in all peri-implantitis specimens, but without evidence of a foreign body reaction suggestive of a direct pathological effect.[76]

In summary, the available literature shows that titanium particles are commonly detected in both healthy and diseased peri-implant mucosa, and even in gingiva of individuals without titanium implants. Thus, there is poor specificity for the association between the presence of particles and pathology. There is, however, a tendency to find more titanium particles in close proximity to the implant surface[69] and in specimens from diseased sites.[77]

Released titanium particles have the potential to trigger an inflammatory response. Inflammatory cells, biofluids, and bacteria can all influence titanium particle release in a process called biocorrosion and can be further influenced by mechanical friction and wear in a phenomenon called tribocorrosion. Given the intimate and complex relationship between these factors (ie, inflammation, corrosion, particle release, and bacterial composition), the potential role of titanium particles on peri-implant crestal bone loss needs to be considered in the context of biocorrosion and tribocorrosion.

4.2 | Biocorrosion and tribocorrosion

Titanium and its alloys belong to a large group of oxide-passivated metals that also include metals such as stainless steel, nickel, and cobalt and aluminum–based alloys. The inertness of titanium is largely attributed to the excellent corrosion resistance of the titanium oxide layer. Damage to the oxide film can "repair" spontaneously and rapidly if the environment contains oxygen or moisture. These features of titanium render it highly resistant to corrosion. In theory, however, certain acids can still corrode titanium, and the speed of corrosion differs depending on the type of acid. For example, titanium exhibits good corrosion resistance in strongly oxidizing nitric acid, whereas an opposite corrosion behavior is experienced in reducing hydrofluoric acid.[78] There are several types of corrosion, of which galvanic, fretting, pitting/crevice, and environmentally induced cracking are the ones mostly associated with titanium.[79]

Theoretically, corrosion can lead to the breakdown of the titanium oxide layer, and in situations where the titanium oxide layer cannot be repassivated, such as an anaerobic environment, this may consequently lead to exposure of the bare metal to active corrosion and result in the release of titanium particles. The corrosion of titanium in a simulated body fluid environment has been demonstrated *in vitro*, and the elution of titanium ions has been shown to be influenced by immersion time, pH of the solution, acid type, mechanical stimulus, and contact with dissimilar metal.[80] It has been demonstrated that an experimental mixed biofilm initiates a decrease in pH and, therefore, leads to the corrosion of titanium *in vitro*.[81] Further, an *in vitro* study using mouse-derived macrophages has reported that the release of active oxygen species from macrophages can induce ion release from titanium in the absence of wear and fretting.[82] These types of corrosion have been collectively named "biocorrosion" or microbiologically influenced corrosion[83] and can lead to undesirable metal ions and corrosion products. Indeed, there is substantial literature that convincingly shows that acidic environments induced by both bacterial biofilms and resultant inflammatory processes trigger surface oxidation and the release of titanium particles.[13] Additionally, there are also *in vitro* studies showing that certain therapeutic substances commonly used in dentistry—such as bleaching agents of fluoride and hydrogen peroxide–containing mouth rinses—can also reduce the corrosion resistance of titanium alloys or have direct biocorrosive effects.[84–86]

The concept of biocorrosion can be further expanded by considering the influence of mechanical friction/wear, which together contribute to a degradation process called "tribocorrosion." In tribocorrosion, a tribo system has three interrelated components: tribology (friction, wear, and lubrication), corrosion (materials and environmental factors), and biochemistry (the interactions between cells and protein).[87] In terms of possible tribocorrosion in the oral cavity, one can view this as the "irreversible transformation of metal (dental implants and its abutments) caused by simultaneous action of chemical, mechanical (wear), and electrochemical (corrosion) interactions on surface subjected to relative contact movement."[88] It is clear that the unique dental implant environment (ie, nonshedding transmucosal structure residing in a microbial-rich fluid environment with a submucosa connection exposed to mechanical forces) makes tribocorrosion a potential contributing mechanism to peri-implant crestal bone loss.

Tribocorrosion is a frequently explored issue in orthopedics, as the implanted alloplastic implants (ie, total joint replacement) devices are consistently exposed to friction and wear in the presence of potentially corrosive body fluids.[89] Indeed, wear debris and ions released from medical implants and prostheses have been shown to elicit an inflammatory response.[90,91] In orthopedics, the inflammatory response eventually leads to a process called "aseptic loosening," which is a common reason for revision surgery. This has been documented in cases where wear debris derived from an articulate region with various particle sizes ranging between nanometer and millimeter in uncemented metal prostheses can stimulate an immune response and elicit an inflammatory reaction.[92] The tribocorrosion behavior of titanium alloys has been documented in simulated biological environments, with none of the alloys tested found to be immune to tribocorrosion in the *in vitro* setting.[88] One must keep in mind, however, there are several significant differences between the orthopedic and dental setting, in that dental implants are placed within a transmucosal/open environment, not a closed environment, as in the case of total knee/joint replacements. Further, the forces involved and the materials used in orthopedics are different to those in dentistry, and hence these clinical scenarios cannot be directly compared. Interestingly, in dental implantology, aseptic loosening has been associated with zirconia implants but not with titanium implants.[93]

Assuming corrosion by-products (metal particles) are either cleared from the transmucosal environment via the peri-implant crevicular fluid or have accumulated in the surrounding peri-implant tissue, the effect of corrosion by-products on the biofilm is unclear. *In vitro* studies exploring the effect of titanium granules on oral bacterial species have reported conflicting results, with some studies showing limited antimicrobial effects,[94,95] whereas more recent reports have demonstrated significant antibiofilm activity of titanium nanoparticles, either alone or in combination with other nanoparticles.[96,97] Indeed, titanium nanoparticles have been proposed as a commercially viable anti-plaque and anti-biofilm strategy.[98] Nevertheless, currently, the impact of corrosion by-products and titanium particles on bacterial growth is unclear, and so further research is required to understand their possible effect on the formation and composition of biofilms in the peri-implant sulcus.

In summary, wear, corrosion, titanium particles, inflammation, and microorganisms take part in a complex host response to foreign bodies. There is some biological plausibility for a link between corrosion, the presence of titanium particles, and biological complications. However, there are currently insufficient data to support a unidirectional role of titanium corrosion and metal particles in the pathogenesis of peri-implantitis.

5 | CONCLUSIONS

The influence of a foreign body response to the implant material in the etiology of crestal bone loss is both a complex and underexplored area of research in dental implantology that requires further investigation. The available literature supports the following conclusions in relation to the potential role of a foreign body response to the dental implant materials as a risk factor for crestal bone loss:

1. Although titanium, like all implanted biomaterials, elicits an inflammatory response upon implantation and cannot be considered absolutely "inert," the available evidence supports the notion that the osseointegration of titanium dental implants represents a return to tissue homeostasis rather than a chronic inflammatory state that is characteristic of a "foreign body response."
2. There is no evidence for a prominent role of a "foreign body response" (also characterized as "foreign body equilibrium" or a

"mild chronic inflammatory state") to an osseointegrated implant in the pathogenesis of peri-implantitis. The available evidence supports our understanding that the dental plaque biofilm is the key modifiable etiological factor in peri-implantitis and, hence, is the logical frontline target of both preventative and therapeutic interventions.

3. There is a lack of evidence for a unidirectional causative role of corrosion by-products and titanium particles as possible non–plaque-related factors in the etiology of peri-implant disease, although this area remains underexplored and requires further investigation.

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