Article

What is the impact of titanium particles and biocorrosion on implant survival and complications? A critical review

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SUPPLEMENT ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

What is the impact of titanium particles and biocorrosion on implant survival and complications? A critical review

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Results: Titanium particles and degradation products of titanium have been detected in oral and nonoral tissues. Particles are released from surfaces of dental implants because of material degradation in a process called tribocorrosion. It involves mechanical wear and environmental factors, notably contact to chemical agents and interaction with substances produced by adherent biofilm and inflammatory cells. In vitro, titanium particles can interfere with cell function and promote inflammation. A temporal association between exposure to titanium and occurrence of tissue reactions suggested hypersensitivity in a limited number of cases. However, there is poor specificity as the observed reactions could be initiated by other factors associated with the placement of implants. Titanium particles are commonly detected in healthy and diseased peri-implant mucosa alike, at low levels even in gingiva of individuals without titanium implants. Rather than being the trigger of disease, higher concentrations of titanium in peri-implantitis lesions could be the consequence of the presence of biofilms and inflammation.

Conclusion: There is an association between biocorrosion, presence of titanium particles, and biological implant complications, but there is insufficient evidence to prove a unidirectional causal relationship.

KEYWORDS
corrosion, implants, peri-implantitis, titanium

1 | INTRODUCTION

Titanium is a transition metal with a silver color, known for high strength and resistance to corrosion. Its outstanding capacity to incorporate into bone in a phenomenon termed "osseointegration" (Albrektsson, Brånemark, Hansson, & Lindström, 1981) is thought to be a primary requirement for the long-term stability of dental implants. Today, titanium is the predominant material used for oral implants, and over 50 years, various studies have continuously demonstrated their high survival rates (Buser, Sennerby, & De Bruyn, 2017). Nevertheless, concerns have been raised regarding titanium's potential to induce hypersensitivity or inflammatory reactions in

the host tissues which could lead to various complications in certain cases. Recent reports have shown that higher quantities of dissolved titanium were detected in the submucosal biofilm taken from implants with peri-implantitis compared to samples from implants with healthy peri-implant tissues (Safioti, Kotsakis, Pozhitkov, Chung, & Daubert, 2017). Beforehand, higher concentrations of titanium particles were detected in cells exfoliated from the peri-implant mucosa of implants with peri-implantitis than from clinically healthy implants (Olmedo, Nalli, Verdu, Paparella, & Cabrini, 2013). Such findings suggest that the release of titanium particles into the tissues may play a role in the pathogenesis of peri-implant diseases. This issue largely contributes to the debate surrounding the value of alternative implant materials, mainly zirconia nowadays (Cionca, Hashim, & Mombelli, 2017). Allergies and hypersensitivity reactions to titanium implants have been the subject of two reviews (Javed, Al-Hezaimi, Almas, & Romanos, 2013; Siddiqi, Payne, De Silva, & Duncan, 2011). They both concluded that the significance of titanium as a cause of allergic reactions remains unproven, but hypersensitivity reactions could not be entirely ruled out. As a second hypothesis, independent of allergic pathways, debris released from implants may have toxic or pro-inflammatory potential to harm peri-implant tissues (Noronha Oliveira et al., 2018).

The purpose of this review was to compile the current evidence regarding the association between the release of titanium particles and the biologic complications of dental implants.

2 | MATERIAL AND METHODS

For this critical review, we initially searched the U.S. National Institutes of Health free digital archive of biomedical and life sciences journal literature (PubMed) to identify relevant articles up to December 31, 2017, using the terms "corrosion" OR "allergy" OR "hypersensitivity" OR "particles" together with (AND) "titanium" OR "Ti" OR "TiO_2." We then searched the bibliographies of identified publications and previously published review articles on biological implant complications for further potentially relevant articles. We included clinical studies, as well as pertinent in vivo and in vitro experiments. Title and abstract of the articles were first evaluated for relevance by two researchers (AM, NC) independently, followed by a joint discussion by all authors to select the relevant publications.

3 | RESULTS

3.1 | Biological complications of dental implants

Biological complications of oral implants include early failure due to lack of osseointegration, inflammatory lesions limited to the mucosa termed peri-implant mucositis, bone resorption associated with infection termed peri-implantitis, aseptic bone loss, and implant loosening. Several factors have been associated with a higher risk of biological complications. Premature loading, tobacco smoking, and systemic conditions such as diabetes have been associated with early implant loss (De Bruyn & Collaert, 1994; Mombelli & Cionca, 2006). Aseptic bone loss has been linked to overinsertion of implants (Hämmerle, Brägger, Bürgin, & Lang, 1996), insufficient interimplant distance (Tarnow, Cho, & Wallace, 2000), and abutment installation on bone-level implants (Adell, Lekholm, Rockler, & Brånemark, 1981). Factors associated with peri-implantitis and late failures include periodontitis, smoking, and diabetes mellitus (Atieh, Alsabeeha, Faggion, & Duncan, 2013; Bornstein, Cionca, & Mombelli, 2009; Derks & Tomasi, 2015; Heitz-Mayfield & Huynh-Ba, 2009; Karoussis, Kotsovilis, & Fourmousis, 2007; Klokkevold & Han, 2007; Ong et al., 2008; Quirynen, Abarca, Van Assche, Nevins & van Steenberghe, 2007; Safii, Palmer, & Wilson, 2010; Schou, Holmstrup, Worthington, & Esposito, 2006; Stacchi et al., 2016). Furthermore, undisturbed accumulation of bacterial deposits on implants has been shown to stimulate peri-implant mucosal inflammation in a comparable way to plaque-induced gingivitis. Clinical experiments (Meyer et al., 2017; Pontoriero et al., 1994; Salvi et al., 2012; Zitzmann, Berglundh, Marinello, & Lindhe, 2001) have established a cause–effect relationship between biofilm formation and inflammation, with a stronger clinical reaction around implants compared to teeth.

3.2 | Allergies and hypersensitivity reactions linked to implanted titanium

Certain types of metal can cause allergic reactions. Nickel allergy is the most frequent of these conditions and has been well studied (Saito et al., 2016). It mainly presents as a rash or eczema-like patches on skin after prolonged contact. Ni++ cations easily penetrate the skin and bind to proteins, creating an antigenic epitope (Lu et al., 2003). Antigen-presenting cells of the skin (dendritic cells and Langerhans cells) pick up these epitopes, undergo maturation, and migrate to regional lymph nodes. CD4+ T cells are then activated via the major histocompatibility complex (MHC) II (Girolomoni, Gisondi, Ottaviani, & Cavani, 2004). Hence, re-exposure to nickel massively recruits these T cells to the skin, resulting in the clinical signs.

Titanium has a high reactivity toward oxygen and therefore cannot exist freely in its cationic form. Nevertheless, it has been hypothesized that titanium dioxide (TiO_2) may bind with proteins and that these compounds could elicit hypersensitivity reactions. In the nondental field, there are scattered reports of conditions suspected of being allergic or hypersensitivity reactions to implanted titanium, mainly because of their clinical manifestation and a temporal association with the presence of titanium; that is, they occurred after implantation and disappeared once the material was removed. In a typical manner, affected patients have a charged medical history and/or suffer from a severe systemic disease. A recent comprehensive review (Fage, Muris, Jakobsen, & Thyssen, 2016) listed 18 case reports of suspected titanium allergy. Symptoms assumed to be caused by titanium allergy include pruritus, redness, swelling, and vesicular lesions of the skin overlaying implanted devices that

contain titanium such as pacemakers, endo-prostheses, implants, and screws.

As an example (Tamai et al., 2001), a 28-year-old woman with breast cancer who had been treated for atopic dermatitis since her infancy underwent breast-conserving surgery. Titanium clips were placed at the margin of the excision cavity. After 2 months, the patient exhibited a rapid exacerbation of atopic dermatitis. Another patient (Thomas, Bandl, Maier, Summer, & Przybilla, 2006) showed impaired fracture healing after titanium-based osteosynthesis and developed an eczema in the perioperative area. After removal of the titanium material, fracture healing was achieved and the eczema cleared.

In the dental field, the possibility of allergies and hypersensitivity reactions to titanium has been discussed in two reviews (Javed et al., 2013; Siddiqi et al., 2011). A limited number of oral lesions have been suspected of being a reaction to titanium based on their proximity to dental implants, and a temporal association between the exposure to titanium and the presence of the lesion:

- Two patients developed persistent proliferation of the peri-implant soft tissue following mandibular vestibuloplasty and placement of a split-thickness skin graft (Mitchell, Synnott, & VanDercreek, 1990). In both cases, chemotherapeutic agents, good oral hygiene, and a gingivectomy procedure failed to adequately resolve the issue. The condition, however, disappeared once the titanium abutments were replaced with custom-fabricated gold abutments.
- One case, a 49-year-old female patient, developed a marked tissue reaction to six implants placed in the context of a clinical study (du Preez, Butow, & Swart, 2007). Due to the severity, all implants were removed and the peri-implant soft tissues were analyzed histologically. There was a chronic inflammatory response with concomitant fibrosis around all implants as well as a foreign body giant cell reaction around two implants. After the removal of the implants, the soft tissues and bone healed satisfactorily.
- In one case, a facial eczema emerged after placement of two titanium implants for a mandibular overdenture (Egusa, Ko, Shimazu, & Yatani, 2008). Complete remission was achieved by the removal of the titanium material.
- Reactive lesions of the peri-implant mucosa at titanium implants were found in two cases, one diagnosed as pyogenic granuloma and the other as peripheral giant cell granuloma (Olmedo, Paparella, Brandizzi, & Cabrini, 2010). Histological analysis of the removed tissue revealed presence of metal-like particles.

Two studies sought evidence for presence of hypersensitivity or allergy to titanium with patch or blood tests in individuals with titanium implants:

- Cutaneous and epicutaneous tests for titanium allergy were carried out in 35 patients selected from a pool 1,500 of persons with dental implants because of symptoms suggesting an allergic reaction after implant placement, implant failure, a history of other allergies, or heavy titanium exposure during implant surgery (Sicilia et al., 2008). Eighteen of these 35 individuals showed a positive reaction to titanium, while 35 randomly selected control persons tested negative. Five of eight unexplained implant failures tested positive.
- Fifty-six patients with clinical symptoms, suggesting an allergic reaction after placement of titanium implants, were tested using the so-called memory lymphocyte immunostimulation assay (MELISA) against 10 metals including titanium (Müller & Valentine-Thon, 2006). 21 patients tested positive for titanium, 16 were ambiguous, and 19 were negatives. Of the latter, 11 individuals showed lymphocyte reactivity to other metals, including nickel. Conventional patch tests to titanium were also carried out and were all negative. Following removal of the implants, all patients were reported to show a relief of clinical symptoms. 15 patients were tested again and showed a normalization in MELISA reactivity.

Comparing alleged cases of titanium hypersensitivity in the nondental and dental fields, one notes differences in clinical manifestations. Symptoms in the nondental field, such as pruritus, redness, swelling, and vesicular lesions of the skin, are not limited to tissues in direct contact with titanium. In the oral cavity, signs of supposed titanium hypersensitivity are predominantly seen in tissues in direct contact with dental implants.

Oral and nonoral hypersensitivity reactions to titanium could be underreported due to ambiguous clinical signs. On the other hand, pathological alterations of peri-implant tissues could also be caused by factors other than the implant material itself. Titanium surfaces can be contaminated by various substances. The occasional presence of residues of products used in the manufacturing processes, such as cutting fluid, sandblasting powder, or etching agents, cannot be excluded. Detrimental effects of machine oil and other surface contaminants on peri-implant tissues have been demonstrated experimentally (Bonsignore, Goldberg, & Greenfield, 2015; Bonsignore et al., 2011). Contamination is also possible during cleaning, storage, and handling of the implants. Traces of heavy metals, cleaning agents, processing aids, and packaging debris have been detected on implants (Arys et al., 1998; Spiegelberg, 2006).

Comparing potential hypersensitivity reactions to dental implants or implanted devices, one must furthermore take into account that all dental implants are inevitably contaminated by bacteria already during surgery, while this should not be the case for indwelling devices. Adherent lipopolysaccharide and other microbial residues have been shown to interact negatively with peri-implant tissues (Bonsignore, Anderson, Lee, Goldberg, & Greenfield, 2013).

Taken together, the evidence for existence of hypersensitivity or allergy against titanium is weak. It consists essentially in a limited number of cases where a temporal association between exposure to titanium and occurrence of tissue reactions could be demonstrated, and in finding such reactions in tissues in proximity to implanted titanium. It is true that not all biological complications of dental implants can be explained by infection; especially, multiple and/or recurrent

nonintegration, or spontaneous loss of osseointegration, may be suggestive of an adverse tissue reaction to the implanted material. However, most of the Bradford Hill criteria for causation (Hill, 1965) are not satisfied: First, there is no consistency in findings observed by different persons in different places with different samples. Second, there is poor specificity as the observed reactions could be caused by other factors associated with the placement of implants. Coherence between epidemiological and laboratory findings would increase the likelihood of an effect. There are currently two studies (Müller & Valentine-Thon, 2006; Sicilia et al., 2008), presenting results from selected populations. The validity of patch testing can be questioned because it evaluates reactions to epidermal rather than oral mucosal contact. Oral mucosa and skin have different permeability and immunological properties, as reflected in the number of antigen-presenting cells. There is controversy about the validity of the MELISA method, especially with regard to the unclear rate of false-positive results (Cederbrant, Gunnarsson, Hultman, Norda, & Tibbling-Grahn, 1999; Cederbrant, Hultman, Marcusson, & Tibbling, 1997).

Based on the current level of evidence, and the small number of reported cases, it is unlikely that allergy or hypersensitivity to titanium plays a major role in the epidemiology of peri-implant diseases.

3.3 | Titanium particles in the tissues and their origin

Titanium particles and degradation products of titanium have been detected in oral and nonoral tissues. The origin of these particles remains controversial. In patients with dental implants, their origin has been assumed to be the implants. In such patients, particles could be detected in bone, peri-implant soft tissues, submucosal plaque, and even at distance in lymph nodes (Weingart et al., 1994). In an animal experiment (Schliephake, Reiss, Urban, Neukam, & Guckel, 1993), traces of titanium were found 5 months after implant placement in tissue specimens of lungs, kidneys, and liver. Studies suggested titanium particles were disseminated throughout the body via the bloodstream by plasma proteins or phagocytic cells to specific organs like lungs, spleen, liver, or abdominal lymph nodes (Olmedo, Guglielmotti, & Cabrini, 2002; Urban et al., 2000). However, animal experiments have also shown that particles originating from a nondental source can accumulate in the gingival tissues. After injecting male Wistar rats intraperitoneally with a suspension of TiO_2 particles (1.6 g/1,000 g body weight) of different sizes (5 nm, 10 nm, 150 nm), specimens of gingival tissue exhibited agglomerates of nanoparticles, with a predilection on the buccal side (Guglielmotti et al., 2015). When cytologic samples of the peri-implant mucosa from persons with or without titanium or zirconia implants were analyzed for traces of titanium and zirconium using inductively coupled plasma mass spectrometry (Cionca, Hashim, Meyer, Michalet, & Mombelli, 2016), zirconium was only found in patients with zirconia implants, whereas titanium was detected even in individuals without titanium implants. Titanium is an abundant element in the earth's crust, and its salts are widely used in all kinds of products of modern life to obtain white color or to protect from ultraviolet light. Independently of dental implant therapy, every individual living in a developed country is invariably and continually exposed to TiO_2: It is used as micro- or nanoparticles in foods (sweets, candies, chocolate, chewing gum, dairy products, and their substitutes), toothpastes, cosmetics, sunscreens, and even medicine pills (Weir, Westerhoff, Fabricius, Hristovski, & von Goetz, 2012). Oral hygiene procedures massage TiO_2 particles into the gingiva every day. Titanium particles in sunscreens are believed to remain in the top layers of the stratum corneum (Larese Filon, Mauro, Adami, Bovenzi, & Crosera, 2015) but are applied in relatively large quantity on big surfaces.

Elementary titanium reacts strongly and quickly with oxygen and forms a stable and protective layer of TiO_2 on its surface that protects the deeper parts from further oxidization. In fact, under common environmental conditions, for example, exposure to seawater, there is no visible corrosion, even over periods of several years. However, in the oral cavity, titanium may sometimes be exposed to local conditions that may foster corrosion. Several mechanisms have been suggested to be involved in the release of titanium particles from surfaces of dental implants, including mechanical wear, contact with chemical agents, and effects of biofilm adhesion.

3.3.1 | Mechanical wear

The oxide layer can be mechanically disrupted, and such damages can result in the release of titanium particles. Mechanical wear of implant surfaces can occur at different instances: during implant placement, during the fitting of a dental prosthesis, due to mechanical cleaning in the context of prevention and therapy of peri-implant infections, and as a result of micromovements of parts of the implant and the suprastructure during function. "Tribocorrosion" is a material degradation process due to the combined effect of friction/wear and corrosion.

The following experiments demonstrated the possibility of titanium release during implant placement:

- An in vitro microstructural analysis of dental implants subjected to insertion torque and pullout tests suggested that inserting and removing implants reduced the oxide layer (Valente, Lepri, & Reis, 2014).
- An in vitro study showed that the insertion of oral implants could provoke the release of particles by stripping them off the surface (Deppe et al., 2017). Three implant systems with different surface roughness were placed in porcine bone of Class I according to Misch classification (Misch, 1999). The mean maximal roughness, the mean surface roughness (Sa), and the developed surface area ratio were highly modified during implant placement into the bone. Differences were observed according to whether the implant surface was large-grit-blasted and acid-etched or anodized. For acid-etched implants, a decrease of the mean Sa was noted, especially in the apical region (−10.4%). In contrast, on anodized implants, the mean surface roughness increased (+5.7%) indicating a destruction of the surface.

- Another group investigated the impact of mechanical forces on surfaces of sandblasted acid-etched implants placed in polyurethane foam blocks (Sridhar et al., 2016). Exfoliated material was detected with microscopic analysis on the osteotomy walls. However, diffraction analysis did not identify these particles as metal elements but as debris from the drilling procedure. In this context, the torsional forces created during the implant insertion could have an effect on the premature damage of the surface.
- An animal study confirmed titanium contamination of peri-implant bone after the placement of implants in the mandible of minipigs (Meyer et al., 2006). Scanning electron microscopy revealed titanium particles were more abundant in the crestal part of the bone and around implants with a rougher surface (Sa: 2.2 μm). Wear was less important on surfaces with a roughness of 1.5 μm and 0.4 μm.
- In recent times, another group of authors confirmed these findings (Suarez-Lopez Del Amo et al., 2017). They tested five different implant surfaces (dual-acid-etched, fluoride-modified, sandblasted large-grit acid-etched/hydrophilic sandblasted large-grit acid-etched, phosphate-enriched titanium oxide, and large grit). All systems showed small angular or round elongated titanium debris in the crestal part of the osteotomy site. In contrast, another study could not verify these conclusions (Wennerberg et al., 2004). After the insertion of implants in rabbit tibia, these authors did not find an association between roughness and ion release.

The possibility of titanium release as a result of micromovements during function has been assessed in several experiments and factors influencing the degree of titanium release have been identified. Micromotion could promote wear of the implant and the abutment, which would increase the microgap and allow bacterial microleakage:

- Different implant systems with different implant–abutment connections were tested in vitro using a cycling loading protocol (Blum et al., 2015). Variations of the microgap and wear patterns were analyzed. After 200,000 cycles, all implants presented an increase in microgap size in the lower and/or upper part of the implant–abutment connection depending on the system. Signs of wear were visualized by scanning electron microscopy as well as particles dispersed throughout the tribolayer. Particles size was in the range of 2–80 μm. Two wear mechanisms were described: fretting-wear, referring to chipping, and adhesive wear, referring to plastic deformation. It was stressed that in clinical conditions, bone and the oral environment would have a strong influence on the wear pattern. Bone owns resilience properties to mechanical loading, and oral fluids (saliva, peri-implant crevicular fluid, and blood) are natural lubricants that modify friction resistance.
- In another in vitro study, zirconia abutments inserted in titanium implants showed a higher rate of wear (8.3 times) and titanium release than titanium abutments in titanium implants (Klotz, Taylor, & Goldberg, 2011). The analysis could quantify the wear of all the abutments with an average of 15.8×10^3 μm^2 for titanium and 131.8×10^3 μm^2 for zirconia. However, it was reported that after 250,000 cycles, the wear rate slowed down.
- A comparative in vitro study on wear at titanium–titanium and titanium–zirconia implant–abutment interfaces demonstrated that the deformation energy will be distributed to the material with the lower elasticity modulus if two different materials are used (Stimmelmayr et al., 2012).
- Implant–abutment contact surfaces and microgap measurements of different implant connections under three-dimensional X-ray microtomography revealed a misfit between the implant and the abutment resulting in a gap in the range of 0.1 to 10 μm (Scarano et al., 2016). Micromotion and the size of the microgap between connected parts are interrelated and together have been shown to influence the amount of wear as well as marginal bone loss around implants (Liu & Wang, 2017).
- Further parameters determining micromotion at the implant–abutment interface were analyzed (Karl & Taylor, 2014). The magnitude of micromotion (1.52 to 94.00 μm) depended on the tightening torque, antirotational features of the implant system, cast abutments, and the CAD-CAM manufacturing process.

Prophylaxis and therapy of peri-implant mucositis and peri-implantitis involve cleaning of implant surfaces exposed to the oral environment with mechanical and chemical means. For the treatment of advanced peri-implant lesion, some clinicians even advocate the macroscopic modification of the implant surface with rotary instruments in the context of a surgical intervention (Ramel et al., 2016; Schwarz, John, & Becker, 2017). Different sequences of rotary instruments were tested to achieve a smooth surface (Bollen et al., 1996; Ramel et al., 2016). Such procedures inevitably contaminate the surrounding tissues with large amounts of titanium particles and abrasion debris of polishing instruments. Titanium contamination of bone and connective tissue after "implantoplasty" with rotary instruments has been clearly demonstrated (Schwarz, Sahm, Iglhaut, & Becker, 2011). Histologic examinations of peri-implant tissues revealed the presence of a localized mixed chronic inflammatory cell infiltrate dominated by plasma cells and lymphocytes after such therapy. Nevertheless, the same authors did not report any clinical adverse events related to the presence of those particles (Schwarz et al., 2011). New devices were developed to offer a mechanical decontamination with less surface damage. In vitro studies have demonstrated titanium brushes, laser and air powder abrasion might be alternatives to curettes, rotating burs, and ultrasonic devices (Al-Hashedi, Laurenti, Benhamou, & Tamimi, 2017; John, Becker, & Schwarz, 2014; Sahrmann et al., 2015). To what extent these procedures provoke release of titanium particles is currently not known.

3.3.2 | Chemical agents

Some chemical agents can decrease the protection of the oxide layer and initiate a corrosion process. That might occur in contact with products used for dental prophylaxis or treatment that contain acid

or fluoride, or in contact with bacterial biofilms that ferment dietary sugars to organic acids.

An in vitro study investigated the effects of chemical agents on commercially pure titanium and on titanium alloy (Ti-6Al-4V) after immersion and surface rubbing (Wheelis et al., 2016). Severe discoloration and pitting were observed in specimens treated by rubbing with peroxyacetic acid (35%), hydrogen peroxide (15%), citric acid doxycycline (50%), tetracycline (50%), and chlorhexidine (0.12%, 1%). Hydrogen peroxide (3%) and sodium fluoride (0.12%, 0.2%. 1.1%) did not show alterations of the surface. During the immersion phase, only peroxyacetic acid, hydrogen peroxide (15%), citric acid, tetracycline, and doxycycline exhibited damages on the surface. Energy-dispersive spectroscopy analysis detected titanium on the swabs on all rubbing treatments. The combination of acidic solution and mechanical friction might generate damages to the implant surfaces. Another group of authors indicated that chemotherapeutic agents altered the wettability of the surface and chlorhexidine 0.12% produced cytotoxic effects on the surface potentially compromising its biocompatibility (Kotsakis et al., 2016).

In immersion tests (Barao et al., 2012; Strietzel, Hosch, Kalbfleisch, & Buch, 1998), the commonly very low ion release from titanium markedly increased in the presence of fluoride and at low pH. Different patterns of corrosion were observed when titanium grade II or IV implants were in contact with saliva containing F^- ions (Souza et al., 2015). It was suggested that the fluoride ions were incorporated in the oxide layer decreasing its protective properties. Commercially pure titanium had a better resistance to corrosion and exposed pitting corrosion, whereas Ti-6Al-4V implants presented a more generalized distribution of the corrosion on their surface. The more the environment was acidic, the less the concentration of F^- had to be high. A threshold of 200–9,000 ppm NaF at pH 3.5–7.0 was estimated for corrosion of pure titanium (Nakagawa, Matsuya, & Udoh, 2002). Other experiments on bleaching agents demonstrated titanium specimens immersed in 35% hydrogen peroxide showed significantly more microscopic changes in the surface topography of than those in 16% carbamide peroxide (Faverani et al., 2014). Furthermore, a synergistic interaction was reported between albumin and H_20_2, two factors present in the peri-implant environment, in accelerating the rate of corrosion of titanium grade IV at physiological pH and temperature (Yu, Addison, & Davenport, 2015).

Antimicrobial mouthwashes are commonly used after implant placement and peri-implantitis treatment (Heitz-Mayfield & Mombelli, 2014). Corrosion kinetics were analyzed after immersion of Ti-6Al-V disks into different solutions (0.12% chlorhexidine digluconate, 0.05% cetylpyridinium chloride, 3% hydrogen peroxide, and artificial saliva) during 14 days (Faverani et al., 2014). Analysis by electrochemical impedance spectroscopy showed a decrease in corrosion resistance only for specimens exposed to 3% hydrogen peroxide. The same observation was made for changes in surface topography. 0.12% chlorhexidine digluconate and 0.05% cetylpyridinium chloride did not change any of the parameters. In contrast, it was shown 0.2% chlorhexidine digluconate might induce pitting corrosion (Quaranta, Ronconi, Di Carlo, Vozza, & Quaranta, 2010). Concentrations seemed to be the cause of this difference.

Corrosion reactions could also be provoked by coupling titanium with more corrodible dental alloys, that is, amalgam fillings (Ravnholt, 1988). Furthermore, the stability of the oxide coating depends on the electrode potential, which can be affected by substances released by bacteria and host cells in inflammation. The most striking evidence of titanium release is "metallosis," a dark tissue discoloration in tissues adjacent to medical implants, specifically joint replacements (Romesburg, Wasserman, & Schoppe, 2010).

3.3.3 | Bacterial biofilm

In contrast to indwelling devices, dental implants are permanently exposed to an environment containing large amounts of microorganisms. Adherent bacterial biofilms develop on all implant surfaces in the oral cavity (Fürst, Salvi, Lang, & Persson, 2007; Mombelli, Marxer, Gaberthüel, Grander, & Lang, 1995). As these biofilms develop, the bacteria modify their environmental conditions, notably with regard to pH and the concentration of oxygen (Marsh, Moter, & Devine, 2011), and promote inflammatory reactions in adjacent host tissues (Meyer et al., 2017). Bacteria are not only found on the outer implant surface, but also in spaces between the implant body and secondary parts, such as screws, abutments, and prosthesis (Cosyn, Van Aelst, Collaert, Persson, & De Bruyn, 2011; Keller, Brägger, & Mombelli, 1998). Contamination of inner spaces occurs either during the insertion of the secondary parts or later through microgaps between components (Persson, Lekholm, Leonhardt, Dahlen, & Lindhe, 1996).

Bacteria play a prominent role in the initiation of corrosion. The effect of early colonization of planktonic bacteria on titanium surfaces of implants has been investigated (Sridhar et al., 2015). Large-grit, sandblasted, and acid-etched implants were immersed in suspensions of *Streptococcus mutans* for 60 days. *S. mutans* is known for its lactic acid production and as an early colonizer. After only 2 days, discoloration was noted on the surface. After 22 days, corrosion features were observed in the form of microscopic deformation, discoloration, mild rusting along the surface of the implants, and pitting deformations. After 60 days, signs of corrosion were more pronounced with an exposition of the bulk titanium in certain regions leading to dissolution of metal ions. In other experiments, lipopolysaccharide (LPS) from bacteria accelerated the ion exchange between titanium and saliva, thereby reducing the resistance to corrosion and increasing the surface roughness of titanium (commercially pure and grade IV) (Mathew et al., 2012). Other in vitro experiments showed that LPS and pH affected the corrosive behavior of titanium. In general, lower pH and higher LPS concentration accelerated titanium corrosion (Barao et al., 2011).

An in vitro study showed increased bacteria adhesion on implants immersed in a fluorinated medium (1,500 ppm, pH 5.5), in comparison with a control solution (Correa, Pires, Fernandes-Filho, Sartori, & Vaz, 2009). An increase in surface roughness of titanium as a consequence of corrosion was also reported by other authors

(Mabilleau et al., 2006; Morgan & Wilson, 2001). In turn, the effect of surface roughness on early in vivo biofilm formation on titanium was demonstrated as well (Rimondini et al., 1997). It is conceivable that a roughened surface enhances the accumulation of bacteria, thereby inducing peri-implant mucositis and sustaining the process of further corrosion. Thus, corrosion could be seen as a contributing factor for peri-implantitis. In contrast, it has been speculated that biofilm might play the role of a lubricant lowering friction forces to a certain level, thereby decreasing corrosion due to wear (Souza et al., 2010).

The examination of the surface of five titanium dental implants, retrieved due to peri-implantitis, with SEM and energy-dispersive X-ray spectrometry, indicated that all implants had been exposed to very acidic environments, which, in combination with normal mechanical function, led to marked discoloration, pitting attack, cracking, and fretting-crevice corrosion (Rodrigues et al., 2013). A histological analysis of 272 implants retrieved for biological complications during a period of 16 years revealed loss of titanium from the surface and from the internal threads, together with the presence of bacteria in the microgap and in the internal portions of the implants (Scarano et al., 2005). In recent times, another group compared levels of dissolved titanium in submucosal plaque samples from 30 patients, collected around 20 implants with and 20 without peri-implantitis (Safioti et al., 2017). Samples from diseased sites contained more bacteria and displayed higher levels of titanium particles than specimens from healthy sites.

Taken together, these studies convincingly demonstrate that acidic environments induced by bacterial biofilms and/or inflammatory processes trigger surface oxidation and release of titanium particles.

3.4 | Interactions of titanium particles with hard and soft tissues

Several in vitro experiments assessed effects of titanium ions or particles on bone and soft tissue that may play a role in implant stability.

3.4.1 | Bone

In orthopedics, aseptic implant loosening is the major complication. It is caused by wear debris and is characterized by an osteolysis at the bone–prosthesis interface (Marshall, Ries, & Paprosky, 2008). It has been suggested that titanium debris can disturb the balance between bone formation and bone resorption in two ways: directly, by differentially activating osteoclasts and osteoblasts (Wang, Ferguson, Quinn, Simpson, & Athanasou, 1997), or indirectly, by stimulating the secretion of inflammatory cytokines produced by macrophages and lymphocytes (Obando-Pereda, Fischer, & Stach-Machado, 2014; Pioletti, Takei, Kwon, Wood, & Sung, 1999; Wachi, Shuto, Shinohara, Matono, & Makihira, 2015).

Pioletti et al. (1999) revealed cytotoxic effects of titanium particles phagocytosed by osteoblasts. The viability of the osteoblasts was influenced by the concentration of titanium particles of less than 5 μm. At low concentration (0.05%), osteoblasts were not affected. However, at higher concentrations (0.15% to 1%), the direct contact of titanium particles with osteoblasts significantly decreased their viability. A phagocytic process of the particles inducing cell necrosis was observed. A titanium particle concentration of 1% increased the proportion of apoptotic cells to 50%. Release of cytotoxic products by osteoblasts co-cultured with particles was also shown.

The effect of particle size on osteoblast function was analyzed by Choi et al. (2005). Four size groups were evaluated: group I (<1.5 μm), group II (≥1.5 μm and <5.0 μm), group III (≥5.0 μm and <10 μm) and group IV (≥10.0 μm and <15 μm). In all groups, osteoblast adhesion and proliferation were reduced. In groups I, II and III, particles were phagocytosed and decreased the osteoblast viability. Particles >1.5 μm increased the expression of receptor activator of nuclear factor κB ligand (RANKL) more than larger particles. However, the proteolytic activities of matrix metalloproteinases (MMP) 2 and 9 increased with the size of the particles. Groups III and IV reduced the adhesion capability of the osteoblasts.

Other authors reported that titanium ions could influence osteoclasts differentiation by affecting the expression of receptor activator of nuclear factor κB ligand (RANKL) and osteoprotegerin (OPG) in osteoblastic cells in vitro (Koide, Maeda, Roccisana, Kawanabe, & Reddy, 2003). Furthermore, it was shown that human osteoclast precursors in contact to titanium may differentiate to form mature osteoclasts and that the mature cells in turn have the potential to corrode the metal substrate and take up particles (Cadosch et al., 2010).

A recent study demonstrated that a titanium concentration of 9 ppm exposed to *Porphyromonas gingivalis*-lipopolysaccharide (PG-LPS) increased the mRNA expression and protein accumulation of chemokine (C-C motif) ligand 2 (CCL2) and the ratio RANKL/OPG in the gingival tissues and in the bone (Wachi et al., 2015). The authors suggested that titanium ions in a noncytotoxic concentration activated the infiltration of monocytes and the differentiation of osteoclasts. With this pathway, titanium ions might be involved in inflammatory reaction and bone resorption observed in mucositis and peri-implantitis. In contrast, a study showed that titanium ions at concentration between 1 and 9 ppm did not affect the viability of osteoblasts, osteoclasts, and gingival epithelial cells (Mine et al., 2010). Only a concentration of 9 ppm increased the expression of RANKL mRNA in osteoblasts and not in epithelial cells.

Pettersson et al. (2017) showed that titanium particles generate a pro-inflammatory response in macrophages. The filtration of a titanium solution (pore size 0.22 μm) deleted the effect on macrophages but did not lower cytotoxicity at higher concentration. The authors described the need of a primary and a secondary signal for activation of IL-1β. Titanium particles (25 μm) alone had a limited effect on the secretion of IL-1β, IL-6, IL-8, IL-10, interferon-γ, and granulocyte–macrophage colony-stimulating factor. In cell cultures primed with *Escherichia coli* LPS (100 ng/ml), however, titanium particles enhanced the secretion of IL-1β in a dose-dependent manner. LPS was the primary stimulus increasing the expression of pro-IL-1β in the macrophages. Titanium particles were the secondary stimulus

TABLE 1 Studies reporting data on titanium particles in tissues adjacent to dental implants in humans

Study	Pat (*n*)	Imp (*n*)	PP (*n*)	Healthy (*n*)	Control (*n*)	Methods	Imp type
Flatebø et al. (2006)	13	13	0	13	0	Biopsies; LM	Two-stage, 1 system
Fretwurst et al. (2016)	12	12	12	NR	1 zirconia Imp	Biopsies: bone and soft tissue; PLM/SRXRF	4 systems
Halperin-Sternfeld et al. (2016)	14	14	NR; 5 pyogenic granuloma, 9 peripheral cell granuloma	NR	0	Biopsies; LM/PLM	NR
He et al. (2016)	10	7 in 4 Pat	NR	NR	6 Imp in 6 Pat	Biopsies: bone ICP-OES/ LA-ICP-MS/LM/SEM-EDX	2 systems; 3 unknown
Mercan et al. (2013)	30	20	0	30	10	Biopsies; LA-ICP-MS	Two-stage, 1 system
Olmedo et al. (2003)	10	10	NR	NR	NR	Explanted Imp with soft tissues; LM/EDX	NR
Olmedo et al. (2010)	2	2	NR; 2 pyogenic granuloma	NR	NR	Inflammatory tissue resection; LM/ICP-OES	One-stage One-stage
Olmedo et al. (2012)	153	153	0	153	0	Biopsies: oral mucosa; LM/ SEM/EDX	Two-stage, 3 systems
Olmedo et al. (2013)	30	30	15	15	30 Contralateral teeth	Exfoliate cytology; LM/ ICP-MS	Two-stage, 3 systems
Paknejad et al. (2015)	96	96	0	96	0	Biopsies; LM/EDX	Two-stage
Pettersson et al. (2017)	3	18	NR	NR	NR	Biopsies: soft tissue; ICP-MS	1 system
Rodrigues et al. (2013)	5	5	5	NR	NR	Explanted Imp	NR
Safioti et al. (2017)	30	40	20	20	NR	Submucosal plaque samples; ICP-MS	NR
Tawse-Smith et al. (2017)	16	16	0	NR	16 contralateral teeth	Exfoliate cytology; LM/ SEM-EDX/ICP-MS	Immediate Imp placement
Wilson et al. (2015)	31	36	36	NR	NR	Biopsies: soft tissue; LM/ SEM/EDX	NR

Notes. Abt: Abutment; EDX: Energy-dispersive X-ray spectrometry; Gr: Titanium grade; H: Healthy; ICP-MS: Inductively plasma mass spectrometry; ICP-OES: Inductively coupled plasma–optical emission spectrometry; Imp: Implant; LA-ICP-MS: Laser ablation–inductively coupled plasma–mass spectrometry; Level I: Superficial strata of the epithelium; Level IV: Surface of the connective tissue in contact with the cover screw; LM: Light microscopy; NR: Not reported; Pat: Patient; PLM: Polarized light microscopy; PP: Peri-implantitis; SEM: Scanning electron microscopy; SRXRF: Synchrotron radiation X-ray fluorescence spectroscopy; Ti: Titanium.

[a]Number of particles in a tissue area of 12 μm^2. [b]Geometric means and standard deviations with comparison based on linear mixed model using log-transformed data after adding 1. [c]Elemental concentration of titanium in biopsies.

Imp material	Placement to sampling	Imp surface analysis	Presence of Ti particles	Particle size	Particle location	Ti concentration
Gr IV	6 m	NR	100% biopsies	NR	Between collagen fibers	NR
Gr IV; Abt material Gr IV/V	NR	NR	75% samples	NR	NR	4,478–7.53 × 10^5
NR	NR	NR	93% samples (foreign bodies)	NR	Connective tissue	NR
NR	NR	NR	100% samples around Imp	0.5–40 μm	At distance of 556–1,587 μm from Imp surface	Test: 1,940 ± 469 μg/kg bone weight; Control: 634 ± 58 μg/kg bone weight
Gr IV	3 m	NR	100% biopsies	NR	NR	Test: 50.4 μg/g ± 23.5 μg/g; Control: 37.1 μg/g ± 1.0 μg/g
NR	NR	NR	Yes	NR	Inside macrophages	NR
Gr IV	2 m	NR	Yes	NR	Inside and outside cells	NR
NR	12 years	NR	Yes, "metal-like particles"	NR	Inside and outside cells	NR
NR	6 m	NR	41% of biopsies	0.9–3 μm^2	90% of particles at level IV	Level I, X = 551 ± 558[a]; Level IV, X = 460 ± 720[a]
Gr IV	3–63 m	NR	100% samples around Imp	NR	Inside and outside cells	PP: 2.02–2.44 ppb; H: 0.41–0.88 ppb; C: 0 ppb
NR	≥3 m	NR	100% biopsies	<10 or >30 μm	Connective tissue	NR
Gr IV	5 years	NR	100% biopsies	NR	NR	7.3–38.9 μM
1 Imp: Ti6Al4V; 1 Imp: TiNbAl; 3 Imp: NR	NR	Pitting attack, scratching, cracking, bulk exposure	NR	NR	NR	NR
NR	PP: 7.9 ± 4.6 years; H: 8.1 ± 4.3 years	NR	Yes	NR	NR	PP: 0.85 ± 2.47 ng/μl; H: 0.07 ± 0.19 ng/μl
Gr IV	5 years	NR	100% internal area Imp/Abt interface; 90% internal area cervical; 50% external area Imp; 30% external area tooth	NR	NR	Internal area Imp/Abt: 14.168 ± 2.366[b]; Internal area Imp cervical: 4.438 ± 2.220[b]; External area Imp: 2.490 ± 1.588[b]; External area tooth: 1.506 ± 1.875[b]
NR	NR	NR	7/36	9–54 μm	NR	2%–43%[c]

activating the cascade NLPR3 inflammasome caspase-1 and the release of mature IL-1β.

The level of aggregation of particles, their surface area, and their shape may have an impact. In some experiments, aggregates of large particles showed less toxicity and affected gene expression in cells to a lesser degree than nanoparticles (Okuda-Shimazaki, Takaku, Kanehira, Sonezaki, & Taniguchi, 2010). In other studies, titanium particles of 1 to 3 μm triggered a higher TNF-α release by neutrophils than larger particles, and these cells were able to phagocyte the smaller particles better (Kumazawa et al., 2002). Microparticles and nanoparticles could differ in their action on the cells. Nanoparticles were described as more biologically reactive and more potentially harmful than microparticles because of their greater surface-to-volume ratio (Guglielmotti et al., 2015). Nanoparticles could aggregate in a microparticle size range and change their recognition by the host, hence decreasing the inflammatory response. A recent study investigated the nano-bio interactions in a biological environment and the process of nanoparticle internalization by cells (Ribeiro et al., 2016). A coating by specific ions and proteins was observed on TiO_2 nanoparticles (anatase mineral phase, size 25 nm) depending on the nanoparticle reactivity and on the biologic milieu. These biocomplexes, rich in calcium, phosphate, hydroxyapatite and proteins (albumin), were compared to a protein corona formed around other nanoparticles. It was suggested that biocomplexes masked TiO_2 nanoparticles like a "Trojan horse" to facilitate their internalization by osteoblasts. Ca^{++} helped to increase the cell membrane–titanium interphase and the initial phase of cell adhesion to the extracellular substrate. Inside the cells, some DNA damage and repair was noted that was probably due to the oxidative stress triggered by the nanoparticles.

3.4.2 | Soft tissue

Metals in contact with soft tissues undergo electrochemical processes that liberate metal ions. These ions can form complexes with host-derived proteins, which may activate the immune system. The lymphocyte response to serum protein complexed with metal from implant alloy degradation was studied in vitro (Hallab, Mikecz, Vermes, Skipor, & Jacobs, 2001). To simulate naturally occurring metal implant alloy degradation, titanium alloy (Ti-6Al-4V, ASTM F-136) and cobalt chromium molybdenum alloy (Co-Cr-Mo, ASTM F-75) beads were incubated in serum from healthy volunteers. These experiments demonstrated a lymphocyte proliferative response to both titanium and Co-Cr-Mo alloy metalloprotein degradation products. The response was greatest when the metals were complexed with high molecular weight proteins, and stronger with Co-Cr-Mo than titanium alloy complexes.

Pro-inflammatory responses of human blood lymphocytes and monocytes to TiO_2 particles or titanium surfaces have been assessed. In a retrospective evaluation of patients who had received titanium implants, treatment failure was associated with positive IL-1β and TNF-α release assay scores (Jacobi-Gresser, Huesker, & Schutt, 2013). In another study (Thomas, Iglhaut, Wollenberg, Cadosch, & Summer, 2013), 14 healthy individuals without titanium implants and six individuals with titanium implants without complication showed no enhanced reactivity in terms of lymphocyte transformation. In an interesting manner, individuals without implants showed higher cytokine response (IL-1β, IL-6, TNF-α, IL-10) to titanium than individuals with symptom-free implants.

When titanium ions (9 ppm) were injected in a gingival epithelium, an increase in the expression and in the localization of Toll-like receptor-4, a competent receptor for bacterial lipopolysaccharide, was detected (Wachi et al., 2015). Titanium ions competed with bacterial LPS and modulated the response of gingival epithelial cells by changing their sensitivity to oral bacteria. However, titanium ion concentrations higher than 13 ppm significantly decreased the viability of gingival epithelial cells and induced necrosis (Makihira et al., 2010).

Reports have suggested the particles might follow inter- and intracellular routes to reach the connective tissue (Revell, 2006). As epithelium was considered a physical barrier with the capacity of initiating an innate immune response, an in vitro study investigated the influence of titanium particles on the homeostasis of oral epithelial cells (Suarez-Lopez Del Amo et al., 2017). The authors assessed the DNA damage response to titanium particles originating from five different implant surfaces by quantifying BRCA1 and CHK2, two markers of DNA damage and genomic instability. In this in vitro study, not all surfaces generated toxic particles. Titanium particles from implants with surfaces containing phosphate-enriched titanium oxide, or that had been fluoride-modified or grit-blasted were able to activate DNA damage in oral epithelium cells.

Fibroblasts have also demonstrated some reactions to titanium particles (Wei et al., 2005). Fibroblasts increased their RANKL expression through the pathway COX-2/PGE2/EP4/PKA when exposed to particles of diameter 1 to 3 μm. This phenomenon was dose-dependent. Furthermore, at low particle concentration, a proliferation of fibroblasts and a reduction in their proteolytic and collagenolytic activities were observed (Maloney, Smith, Castro, & Schurman, 1993).

When fibroblasts from peri-implant granulation tissue were challenged in vitro with TiO_2 particles, or *P. gingivalis*, or a combination of the particles and the microorganism (Irshad et al., 2013), the combined exposure had the strongest effect on gene expression of tumor necrosis factor (TNF)-α, and protein production of TNF-α, interleukin (IL)-6, and IL-8. Thus, titanium particles may contribute to the exacerbation of inflammation caused by biofilm-associated bacteria in peri-implant tissues.

Not all dental implants are made of commercially pure titanium. Titanium alloys were developed to improve the mechanical and physical properties of the biomaterial (Osman & Swain, 2015). One of the most commonly used is Ti-6Al-4V, an α+β combination alloy containing aluminum and vanadium. Thus, ions/particles other than titanium might be detected in the oral tissues. An in vitro study demonstrated the toxic potential of vanadium on fibroblasts and osteoblasts growth when vanadium concentration increased from 0.2 ppm to 0.5 ppm (Okazaki, 2001). Aluminum

cytotoxicity was influenced by its concentration, surface roughness, and the strength of the oxide film (Okazaki, Katsuda, Furuki, & Tateishi, 1998).

3.5 | Titanium particles in human peri-implant tissues and association with clinical status

Table 1 lists 15 available studies reporting data on titanium particles in tissues adjacent to dental implants in humans. Samples from the following clinical conditions were analyzed: Mucosa overlying titanium cover screws during submerged healing of two-piece implants, mucosa from peri-implantitis lesions, mucosa with marked clinical signs of inflammation, mucosa from implants without clinical signs of pathology, gingiva from healthy teeth. The following methods were used for analysis: microscopy (scanning electron microscopy, SEM; light microscopy, LM; polarized light microscopy, PLM) of retrieved material and soft tissue biopsies, exfoliative cytology of peri-implant mucosa, and spectrometry to quantify metal particles in tissue samples (inductively coupled plasma mass spectrometry, ICP-MS; energy-dispersive X-ray spectrometry, EDX; laser ablation–inductively coupled plasma–mass spectrometry, LA-ICP-MS; inductively coupled plasma–optical emission spectrometry, ICP-OES; synchrotron radiation X-ray fluorescence spectroscopy, SRXRF).

EDX analysis revealed titanium particles phagocytosed by macrophages in the soft tissues around 10 failed implants explanted because of clinical mobility (Olmedo, Fernandez, Guglielmotti, & Cabrini, 2003). Macrophages loaded with metal-like particles were also seen histologically in two cases of pyogenic granuloma in peri-implant mucosa (Olmedo et al., 2010). Metal particles were furthermore detected in 63 of 153 biopsies of oral mucosa adjacent to titanium cover screws of submerged implants harvested 6 months after implant placement, mostly in the zone of the connective tissue in contact with the cover screws (Olmedo et al., 2012). The particles were found intra and extracellularly.

The same authors examined cells exfoliated from the peri-implant mucosa around 15 implants with, and 15 implants without a diagnosis of peri-implantitis for the presence of metal particles (Olmedo et al., 2013). Samples were collected with a microbrush. While controls from teeth were free of particles, all samples of peri-implant mucosa, with or without a diagnosis of peri-implantitis, exhibited particles inside and outside epithelial cells and macrophages. A spectrometric analysis revealed a higher concentration of titanium in the peri-implantitis specimens compared to the healthy ones, while all control samples were negative. These findings suggested that the presence of titanium particles was the result of surface corrosion of the implants, excluding titanium contamination from another source.

Another group of authors compared titanium levels in the mucosa overlaying cover screws of submerged implants for 3 months from 20 patients with gingiva from 10 patients with no implants (Mercan, Bölükbaşı, Bölükbaşı, Yayla, & Cengiz, 2013). Titanium levels were found to vary greatly among patients. Spectrometry showed a higher level of titanium in the test compared to the control group (50.4 μg/g ± 23.5 μg/g vs. 37.1 μg/g ± 1.0 μg/g, respectively), but the difference was not statistically significant.

Gingiva biopsies from another group of 96 patients treated with two-stage approach implants were analyzed histologically, and titanium particles were sought by EDX (Paknejad, Bayani, Yaghobee, Kharazifard, & Jahedmanesh, 2015). All samples presented patches with high density of large titanium particles. Inflammation was observed in all layers of the biopsies, but was most pronounced in the connective tissue contacting the cover screw. A correlation was found between the presence of particles and the level of inflammation. As particles were not exclusively found in the tissue in direct contact with titanium, the authors suggested that keratinocytes could transport titanium particles to more superficial tissue layers.

Biopsies were harvested from 13 patients at time of implant insertion and at abutment connection after 6 months (Flatebø et al., 2006). At month 6, there was evidence for the presence of metal-like particles, with a decrease in density from the connective tissue to the epithelium. At month 6, an inflammatory infiltrate was found in every specimen within the connective tissue facing the cover screw. The ratio inflammatory infiltrate/fibroblasts, however, decreased from baseline to month 6. Thus, there was no direct association between the accumulation of titanium particles and the development of inflammation.

A retrospective study analyzed 36 peri-implant soft tissue biopsies around implants with peri-implantitis (Wilson et al., 2015). Seven samples revealed presence of titanium particles. Among the other foreign particles detected, 19 samples were positive for elements such as Zr, Si, and Al that likely originated from dental cement. The inflammatory infiltrate consisted predominantly of plasma cells.

The presence of titanium elements was studied in bone and soft tissues around implants removed because of advanced peri-implantitis using SRXRF (Fretwurst et al., 2016). 12 titanium implants and one zirconia implant were examined, each coming from a different patient. Nine tissue samples were positive for titanium, of which six at high and 3 at low level. The specimen from the zirconia implant tested negative for titanium and other metals. In an interesting manner, titanium positive samples tested also positive for iron. LM revealed a predominance of lymphocytes and increased numbers of macrophages in soft tissue areas with metallic particles. No correlation could, however, be established statistically between the quantity of titanium particles and the number of macrophages.

A postmortem study analyzed the levels of titanium and other metallic elements in mandibular bone of four subjects with implants (test group) and six subjects without implants (control group) (He et al., 2016). Titanium levels were three times higher in the test than in the control group (1,940 ± 469 μg/kg-bone vs. 634 ± 58 μg/kg bone weight, respectively). ^{47}Ti was the only metallic isotope measured in samples with implants; it was not detected in the control group. The distribution of titanium particles was highest within a 1 mm range of the implant surface. Multinucleated cells, local avital bone, and marrow fibrosis were observed by LM. SEM-EDX identified titanium particles 0.5–40 μm large.

Biopsies of peri-implant mucosa were obtained from three patients treated 5 years earlier with a full-arch bridge on six titanium implants (Pettersson et al., 2017). Tissue specimens were collected from healthy mucosa and from sites with presence of inflammation. All samples were titanium positive by ICP-MS independent of the clinical status. In an in vitro model, the levels measured in vivo could stimulate a pro-inflammatory response.

Sixteen patients with titanium implants, restored with zirconia abutments, were evaluated 5 years after immediate loading (Tawse-Smith et al., 2017). All implants were clinically successful and showed no clinical signs of disease. Presence of titanium particles was determined based on exfoliative cytology. All samples collected at the implant–abutment interface were positive for titanium. Samples collected at the internal cervical area and at the external implant area were 90% and 50% positive, respectively. The gingiva of contralateral teeth was 30% positive. The highest concentrations of titanium particles were found in samples taken at the implant–abutment interface. The spectrometry analysis also identified other metallic elements such as Al, Zr, Au, Ag, and Cu in peri-implant smears. The origin of titanium particles was likely due to wear caused by the zirconia abutment on the titanium implant. The presence of Au, Ag, and Cu was explained by the gold screws retaining the crowns.

A retrospective study analyzed biopsies from 58 patients presenting 14 peri-implant soft tissue reactive lesions (I-RLs) and 44 tooth-associated reactive lesions (T-RLs) (Halperin-Sternfeld, Sabo, & Akrish, 2016). They investigated the presence of foreign bodies by PLM. On the 14 I-RLs, five were diagnosed as peri-implant pyogenic granuloma and nine as peri-implant peripheral giant cell granuloma. Regarding the T-RLs, 21 were tooth-associated pyogenic granulomas and 23 tooth-associated peripheral giant cell granulomas. Foreign bodies were detected in 13 specimens of the 14 I-RLs (93%) and in 18 of the 44 T-RLs (41%). In the connective tissue, particles were isolated or surrounded by multinucleated giant cells. However, because spectrometry was not performed, foreign bodies could not be identified as titanium particles. The authors concluded foreign bodies might play a role in the development of I-RLs.

4 | DISCUSSION AND CONCLUSIONS

Titanium is the predominant material used for oral implants. Despite high strength and good resistance to corrosion, titanium particles and degradation products of titanium have been detected in oral and nonoral tissues in multiple studies. Titanium particles are released from surfaces of dental implants because of mechanical wear, contact to chemical agents, and interaction with substances produced by adherent biofilm and inflammatory cells.

Two types of host reactions may be considered: (a) hypersensitivity and (b) toxic/pro-inflammatory effects. The evidence for existence of hypersensitivity or allergy against titanium consists in a limited number of cases where a temporal association between exposure to titanium and occurrence of tissue reactions could be demonstrated, and in finding such reactions in tissues in proximity to implanted titanium. However, there is poor specificity as the observed reactions could be initiated by other factors associated with the placement of implants.

In vitro experiments have shown the potential of titanium ions or particles to have toxic or pro-inflammatory effects. In vitro research has also identified factors modulating such effects, for example, particle size and association with molecules like LPS. Titanium particles are commonly detected in healthy and diseased peri-implant mucosa alike, and even in gingiva of individuals without titanium implants. Thus, there is poor specificity for the association between presence of particles and pathology. There is a tendency to find more titanium in close proximity of the implant surface and in specimens from diseased sites. However, higher concentrations of titanium in diseased sites could be the consequence of corrosion caused by the activity of inflammatory cells and bacteria present in peri-implantitis lesions.

There is some biological plausibility for a link between corrosion, presence of titanium particles, and biological complications. However, proof for a unidirectional sequence of causative events does not exist. Wear, corrosion, titanium particles, inflammation, and microorganisms take part in a complex host response to foreign bodies with multiple feedback loops: Wear and corrosion together with environmental factors lead to material degradation in a process called tribocorrosion; this process leads to release of titanium particles. Titanium particles interfere with cell function, possibly promoting inflammation under some circumstances. Inflammation causes corrosion; inflammation also alters the composition and function of biofilms (Hajishengallis, 2014). Biofilms cause inflammation, and biofilms cause corrosion.

It must be mentioned that there are also observations that are not in line with this hypothesis: First, metal oxide nanoparticles, especially of TiO_2, possess antimicrobial activity. So-called nano-antibiotics exploiting this phenomenon are currently developed (Khan, Al-Khedhairy, & Musarrat, 2015). Second, in dental implantology, aseptic loosening has been associated rather with zirconia implants than with titanium implants (Cionca, Müller, & Mombelli, 2015). Third, although all currently available protocols for therapy of mucositis and peri-implantitis further contaminate the peri-implant tissues with titanium particles, they have a certain degree of success (Heitz-Mayfield & Mombelli, 2014).

DISCLOSURE

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