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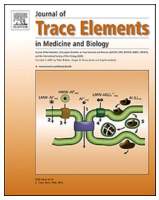

Titanium corrosion products from dental implants and their effect on cells and cytokine release: A review

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ABSTRACT

Introduction: Titanium is considered to be an inert material owing to the ability of the material to form a passive titanium oxide layer. However, once the titanium oxide layer is lost, it can lead to exposure of the underlying titanium substructure and can undergo corrosion.

Summary: The article explores the role of titanium ions and particles from dental implants on cells, cytokine release, and on the systemic redistribution of these particles as well as theories proposed to elucidate the effects of these particles on peri-implant inflammation based on evidence from in-vitro, human, and animal studies. Titanium particles and ions have a pro-inflammatory and cytotoxic effect on cells and promote the release of pro-inflammatory mediators like cytokines. Three theories to explain etiopathogenesis have been proposed, one based on microbial dysbiosis, the second based on titanium particles and ions and the third based on a synergistic effect between microbiome and titanium particles on the host.

Conclusion: There is clear evidence from in-vitro and limited human and animal studies that titanium particles released from dental implants have a detrimental effect on cells directly and through the release of pro-inflammatory cytokines. Future clinical and translational studies are required to clarify the role of titanium particles and ions in peri-implant inflammation and the etiopathogenesis of peri-implantitis.

1. Introduction

Dental implants fabricated out of titanium (Ti) are being widely used in the rehabilitation of edentulous (partial and complete) patients [1]. Clinically, commercially pure Ti and the titanium aluminum vanadium alloy (Ti6Al4V) and titanium zirconium alloy (TiZr) are commonly used to fabricate the endosseous fixture that is inserted into the bone and undergo a process of osseointegration [2]. Ti happens to be the major component as it is capable of forming a titanium oxide (TiO_2) layer that makes the implant biocompatible [3–6]. Our understanding of the ability of Ti to be biocompatible and osseointegrate has evolved [7]. Initial definitions of osseointegration focused on the ability of the implant to undergo functional ankylosis by bone apposition onto its surface [7,8]. However, more recently an alternative definition constituting the dental implant as a foreign body and the process of osseointegration as a host mechanism to shield the dental implant from the surrounding tissues has been proposed [9,10]. The evolution of this concept has led to an understanding that a Ti dental implant elicits a foreign body response and it is in a constant equilibrium state with the host and microbiome that colonizes the surface [9,11,12].

The role of a foreign body eliciting a response from the host was first observed in orthopedics through a process that is aseptic wherein inflammation around the prosthesis due to Ti wear products resulted in its failure [13,14]. Dental implants in function exist in a hostile environment and are exposed to various elements (physical, chemical, and biological) in the oral cavity [15]. The phenomenon that is collectively termed biotribocorossion deals with the study of corrosion related to physical chemical and biological factors. As it pertains to the oral cavity, these factors include electrochemical interactions, friction, micro-movement, host inflammatory response and its products, microbiome and its related products along with chemical factors in the macro and micro-environment surrounding the dental implant [16]. The implants are subjected to macroscopic forces as a result of mastication and other oral structures (tongue, buccal musculature) as well as micro-movements between various components such as Ti abutments and screws [17,18]. Dental implants also are constantly exposed to chemical factors such as fluoride (present in oral hygiene products and dental materials), mouthwashes, and in the case of peri-implantitis

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treatment, chemicals for decontamination such as tetracycline and citric acid. Additionally, dental implants have to withstand biological elements like saliva, peri-implant crevicular fluid, microbiome, and its toxins as well as immune cells that populate the peri-implant sulcus. This delicate equilibrium of several factors can result in the disruption of the TiO_2 layer and lead to the release of Ti particles and ions into surrounding tissues and body fluids. Several studies have evaluated the role of Ti particles and ions on the peri-implant inflammatory processes in animal models, in-vitro, and human studies [19–25]. This paper will aim to comprehensively review the existing literature on the current understanding on the role of Ti particles and ions on peri-implant inflammation, etiopathogenesis of peri-implantitis as well as systemic redistribution of Ti and influence on distant organs. A search was carried out in Pubmed using a combination of keywords "dental implants," "peri-implantitis," "titanium particles," "titanium ions," and "titanium release." The search results were screened and the included studies were stratified into the different sections corresponding to the article. In addition, the reference lists of the included articles were screened for additional studies.

2. Titanium levels and peri-implantitis

Ti implants in the presence of oxygen undergo the formation of a surface TiO_2 layer that is passive and leads to high corrosion resistance, excellent biocompatibility [11], and maintenance of dental implant osseointegration [26]. When the layer is disrupted due to factors such as mechanical wear or chemicals, it can lead to exposure of the Ti substructure and enhanced dissolution of these products into the surrounding peri-implant tissues [16,26–29]. Studies have investigated Ti levels around dental implants with peri-implantitis. Ti in submucosal plaque samples is reported to be higher in peri-implantitis sites when compared to implants diagnosed with peri-implant health [19,30]. Another study reported the correlation between Ti presence in plaque and peri-implant disease status [31]. Additionally, Ti levels in plaque were associated with global deoxyribonucleic acid (DNA) methylation and epigenetic alterations around dental implants [32].

An in-vitro study reported that higher levels of Ti dissolution occurred when dental implants were instrumented for decontamination [21]. The utilization of Ti curettes for cleaning implants diagnosed with peri-implantitis results in high Ti levels in submucosal plaque [20]. Foreign bodies resembling metallic particles are often detected in soft tissue biopsies from peri-implantitis patients [33–37]. Several studies have reported a higher level of Ti particles in peri-implant soft tissues in the presence of peri-implant mucositis [37], peri-implantitis [33,35,36,38,39–41], and from peri-implant bone samples [36]. A translational study found no significant difference in Ti levels in peri-implant crevicular fluid between peri-implant health, peri-implant mucositis, and peri-implantitis but found a significant association with inflammatory mediators [25]. Studies done on saliva found no significant differences between peri-implantitis compared to health [42,43]. The results of these studies can be influenced by changes in microbiome compositions, pH of the local environment, occlusion, patient related factors like smoking, systemic disease, local inflammation, and periodontal status that could account for the differences in findings. Further research is required to clarify the role of Ti particles in translational models of peri-implantitis and to define a threshold level above which it can trigger inflammation and disease progression.

3. Titanium particles, ions, and cellular response

Ti particles and ions can be absorbed into the peri-implant tissues and trigger an inflammatory response resulting in bone resorption [44]. Ti particles can cause changes in inflammatory cells like macrophages, T lymphocytes, and monocytes directly [45]. There is evidence that Ti particles and ions can be internalized through the process of phagocytosis by inflammatory cells lining the peri-implant connective tissue [46] and the intra-cellular uptake of Ti particles by other cells has also been demonstrated [47]. Neutrophils are considered to play a central role in modulating inflammation and this is achieved by the release of reactive oxygen species (ROS). The highest concentration of ROS is released by neutrophils compared to other phagocytes. The released ROS also plays a part in the recruitment of neutrophils which is the principal step of the inflammatory process (46). Neutrophils can phagocytose metallic particles that are smaller than 5 microns due to the size of the cells (Fig. 1)[48]. In an in-vitro study, it was found that smaller particles in the micron range produced higher toxicity and increased inflammation compared to larger particles [49]. Since these smaller particles are ingested by the cells, it promotes a greater cellular and molecular response [48]. In an in-vitro experiment, it was shown that both macrophages and human gingival fibroblasts are also capable of internalizing the Ti particles into the cell [50].

Macrophages in response to the phagocytosis of Ti particles release pro-inflammatory cytokines [51–53]. Macrophages can also independently phagocytose particles less than 10 microns (Fig. 1) [54]. An exfoliative cytology study confirmed that Ti particles are detected within the macrophages [35]. Additionally, there have been reports that macrophages tend to have a greater differentiation towards the M1 phenotype polarization in response to Ti particles and inflammation [45,55]. The M1 macrophage phenotype can result in the activation of osteoclasts resulting in peri-implant bone resorption [56,57]. In the presence of larger Ti particles, the inflammatory cells form multinucleated giant cells that can phagocytose the particles (Fig. 1) [58]. When even the multinucleated giant cells are unable to clear off the Ti particle debris, there is a switch towards additional macrophage recruitment which triggers an extracellular release of enzymes in an attempt to degrade the Ti particles [54].

Ti concentrations of 0.1 mg/ml have a cytotoxic effect on fibroblasts and at higher concentrations on osteoblasts. The particles released during implantoplasty of Ti6Al4V alloys when exposed to in-vitro cell lines resulted in a significant reduction in the viability of human gingival fibroblasts after 10 days in culture [59]. When Ti6Al4V alloy (a common alloy used for making dental implants) is in a pristine condition without wear, the implanted material does not cause a cytotoxic effect [60]. However, when corrosion is induced or in its particulate form, cytotoxic effects on fibroblasts have been observed [60–62]. Micron and submicron Ti debris also have a pro-apoptotic effect on osteoblast cultures [63]. Ti alloy (Ti6Al4V and Titanium zirconium molybdenum alloys) based wear particles affected osteoblasts by reducing viability and metabolism as well as a significant increase in production of cytokines such as Prostaglandin E2 (PGE2) after 3 days of exposure and Interleukin −6 (IL – 6) after 7 days of exposure. The osteoblasts can internalize the Ti debris [64] and Ti particles also enhance pre-osteoblast adhesion through ROS generation [65]. In an animal model, osteoblasts exposed to wear particles containing Ti, aluminum, and vanadium (V) showed reduced cell viability starting as early as 24 hours and an increase in cytokines such as IL – 6, Interleukin – 8 (IL-8), cyclooxygenase 2, and receptor activator of nuclear factor kappa beta ligand (RANK-L) secretion [66]. Another in-vitro study reported cytotoxic effects on osteoblasts from the particles released during implantoplasty [67]. Ultrasonic scaling of implants on the other hand resulted in osteoclastogenesis and increased inflammation attributed to the response of macrophages to the generated Ti debris after scaling [68]. The compatibility and cytotoxicity of implant surfaces after treatment with Ti brushes results in surface damage, reduction of osteo compatibility of treated surfaces, and cytotoxicity of fibroblasts to particles released suggesting that protocols aimed at reducing microbial load on dental implant surfaces may have a detrimental effect on peri-implant cells due to surface damage and the release of Ti debris [21].

In an exfoliative cytology study in patients with peri-implantitis, metal-like particles were present inside the epithelial cells [35]. Oral epithelial cells in contact with Ti particles showed an activation of the DNA damage response upon exposure for 48 hours [69]. In an in-vitro

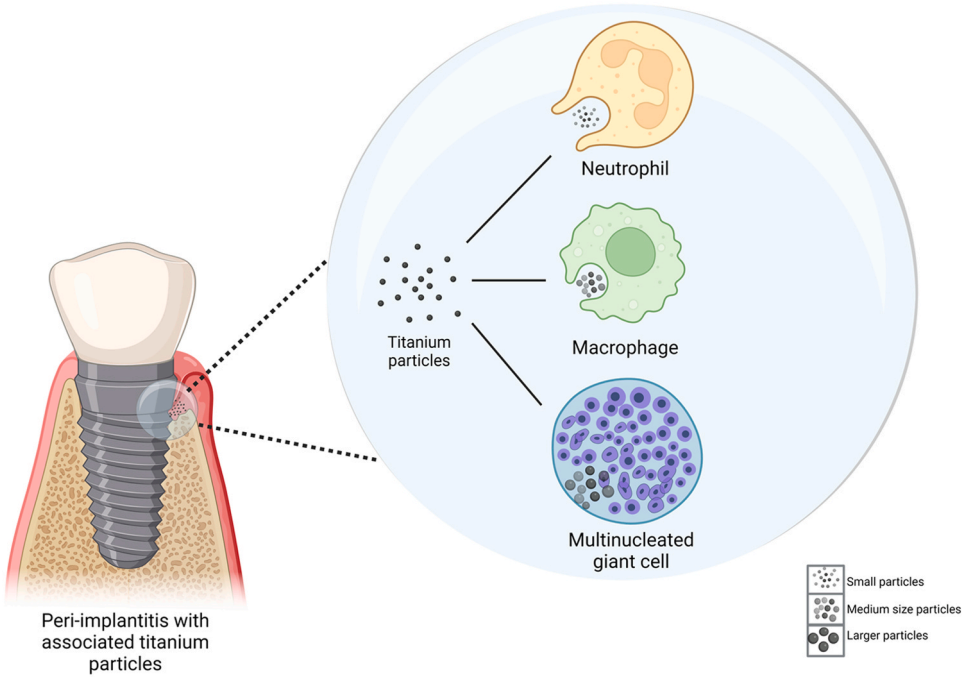

Fig. 1. Fig. 1 is a schematic representation of the influence of titanium particle size on the inflammatory cells. Smaller particles are phagocytosed by neutrophils, medium sized particles are phagocytosed by macrophages and larger particles are phagocytosed by multinucleated giant cells (Created with BioRender.com).

study, it was noted that gingival epithelial like cells when exposed to Ti ions resulted in reduced viability and increased lactase dehydrogenase secretion and this increased the sensitivity of the cells to *Porphyromonas gingivalis (P. gingivalis:a common pathogen in periodontitis and peri--implantitis)* lipopolysaccharide (LPS) [70]. This damage to epithelial cells can compromise the epithelial integrity of the peri-implant sulcus making it more prone to the ingress of bacteria and its toxins [69]. An animal study corroborated these findings and reported that epithelial cells exposed to LPS may have increased susceptibility in the presence of Ti ions [71]. The effect of submicron Ti particles on human mesenchymal stem cells revealed induction of apoptosis and elevation of proteins such as tumor protein p53 [72]. In-vitro studies on the effect of nano-particles of Ti showed an intra-nuclear cell uptake in periodontal ligament cells [73]. Furthermore, a greater number of regulatory T cells were detected around failed dental implants [24].

Apart from a direct effect on cells, Ti particles and ions can cause a foreign body reaction resulting in lesions with varying diagnosis that mimic peri-implant lesions. Several studies have reported that there is an increase in the inflammatory infiltrate in the connective tissue as a result of a foreign body reaction to Ti particles [33,36,38,41]. These findings have been implicated as a biological cause of faster progression of peri-implant lesions compared to periodontitis [74]. Apart from this, foreign bodies have been consistently implicated in lesions such as pyogenic granuloma [75–77], peripheral giant cell granuloma [78–86], squamous cell carcinoma [87–89], hypersensitivity reactions [90] and a possible role in rare lesions such as plasmacytoma [91].

4. Titanium particles, ions, host response, and cytokine release

The peri-implant tissues surrounding an implant may become inflamed when Ti ions or microparticles are discharged into them. These Ti particles have a two-fold effect: one is through the direct effect on cells (as seen earlier) and the second is by inducing cells to secrete pro-inflammatory cytokines [92,93]. Parallelly, endogenous proteins and Ti ions (haptens), because of their strong affinity for proteins, combine to form antigenic molecules [94] which elicits a reaction from the immune cells triggering a release of pro-inflammatory cytokines. These changes can occur through the activation of inflammasomes like NLR family pyrin domain containing 3 (NLRP3) [51] and Caspase 1 pathways [52]. NLRP3 inflammasome activation can cause a release of factors like Interleukin-1 beta (IL-1β) [95]. Caspase 1 pathways can lead to activation of factors like IL-1β and IL-8 [52]. In a clinical cross-sectional study, it was found that Ti levels were significantly associated with interleukins (IL) such as IL-1β, IL-2, IL-4, IL-8, IL-13, and interferon-gamma (INF- γ) levels after adjustment for peri-implant health status [25]. A study on biopsy samples taken from peri-implantitis sites reported a higher proportion of RANK-L, transforming growth factor beta 1 (TGF-β1), and IL-33 adjacent to Ti particles [41]. In a study of exposure of venous blood of patients with dental implants, it was found that if macrophages in venous blood stimulated the production of TNF-α over 40 pg/ml and/or the IL-1β level over 30 pg/ml, there was a greater chance of that patient being diagnosed with peri-implantitis [96]. In-vitro studies revealed that Ti particles that are in the micron size induced macrophages to release factors such as nuclear factor kappa B (NF-kB), MyD88, and TIR-domain-containing adaptor-inducing beta interferon (TRIF) [97]. MyD88 is capable of activating the pathways of signaling of immune cells [98], TRIF is involved in the activation of the alternative pathway and release of mediators like INF-γ [97] and NF-kB is involved in the activation of a pro-inflammatory pathway, [99] ultimately leading to tissue damage. Macrophages exposed to Ti particles showed a greater increase in pro-inflammatory mediators (IL-1β, IL-6, TNF-α, INF γ) and a smaller increase in anti-inflammatory mediators (Interleukin 1 alpha and IL-10) showing a response similar to bacterial lipo-polysaccharides in in-vitro cultures [100]. Another in-vitro study reported that there was an increase in IL-18, IL-1, IL-8, and chemokine ligand 3 (CCL3) released by macrophages exposed to TiO_2 particles [24]. Ti particles also induce monocytes and macrophages to release factors such as tumor necrosis factor-alpha (TNF-α), IL-1β among others [51–53]. Metal particles from TI6Al4V implants released during implantoplasty caused an increase in the secretion of pro-inflammatory cytokines from cells [101]. Specifically, macrophages released increasing amounts of TNF-α, IL-1 β, and lowered TGF-β, IL-10, and Cluster of Differentiation 206 (CD206 mannose receptor: a factor that can mediate phagocytosis) levels [101]. Ti ions in an in-vitro study

stimulated IL-1β release and inflammasome activation in macrophages which was greater when the macrophages were exposed to LPS [52]. Also, macrophages stimulated with TiO2 particles less than 5 microns in size induced the expression of genes controlling pro-inflammation (messenger ribonucleic acid of TNF-α, IL-1β, and IL-6), and this effect was further enhanced when exposed to LPS [102]. TNF-α and IL-1β have a pro-osteolytic effect and through effects on RANK-L production causes bone resorption [51–53,103].

Osteoblasts on the other hand respond by releasing potent factors such as PGE2. PGE2 in turn reduces the secretion of OPG thereby resulting in pro-osteoclastic pathways [53,103]. There appears to be a dual-fold effect of Ti particles by inhibiting bone formation and inducing osteoclast-mediated bone resorption through TNF-α and IL-6 pathways [104]. Osteoblast like osteosarcoma cells in an in-vitro model stimulated the release of IL-1, IL-6, and IL-18 when exposed to commercially pure Ti, Ti6Al4V and oxide blasted Ti discs. They showed that Ti6Al4V had the least response compared to other types [105]. When bone marrow-derived mesenchymal stem cells were exposed to the Ti particles, it was observed that there was a significant decrease in osteocalcin and RUNx2 expression [101]. In another in-vitro study, Jurkat T cells (cells used to study T cell signaling) were shown to have increased IL-1β secretion when exposed to Ti particles [106]. The effect of Ti particles on fibroblasts showed an increase in the release of factors such as IL-1β, IL-6, and IL-10 suggesting a complex pathway through both pro and anti-inflammatory pathways in play [103]. In an in-vitro study, it was observed that fibroblasts exposed to Ti particles released higher ROS and matrix metalloproteinases and an imbalance in mitochondrial function along with dysregulation of mesenchymal stem cells [46]. It is also shown that TiO_2 particles when exposed to peri-implant fibroblasts at sub-toxic levels not only influenced secretion of pro-inflammatory cytokines (TNF-α, IL-6, and IL-8) but also had a synergistic pro-inflammatory effect when challenged with *P. gingivalis* [22]. These findings suggest that Ti particles have a dual fold effect by not only increasing pro-inflammatory cytokine release from fibroblasts and immune cells but also priming them for a greater response when challenged with bacteria and its products like LPS.

5. Titanium particles, ions on distant organs

In 2006, the International Agency for Research on Cancer reclassified TiO_2 nanoparticles as possibly carcinogenic to humans [107]. Migration of Ti and TiO2 particles that are micro or nano-scale via the bloodstream can reach and accumulate in distant organs like the lungs and spleen. In an in-vitro study, splenocytes showed higher upregulation of cytokines like IL-1β, IL-6, IL-10, TNF-α, and INF-γ and granulocyte-macrophage colony stimulating factor in the presence of Ti ions and LPS from periodontopathic bacteria, suggesting the susceptibility of cells from distant organs to Ti and LPS [108]. Another study reported that Ti particles may induce inflammation resulting in fatty degeneration and osteonecrotic medullary changes in the bone marrow that may have implications for other chronic systemic conditions [109]. A study done on an animal model reported that intraperitoneal injection of soluble Ti (titanium citrate) and insoluble TiO_2 particles resulted in different patterns of storage with soluble Ti transported to distant organs such as the spleen, liver, kidneys and lungs with TiO_2 concentrating in lung tissues [110]. Another animal model study on mice reported the systemic redistribution after intra-peritoneal injection of TiO_2 nanoparticles and noted evidence of accumulation in distal organs like the liver, kidney, spleen, lung, brain and heart [111]. High doses of TiO_2 nanoparticles injected intra-peritoneally evaluated up to 14 days post exposure resulted in high accumulation in the spleen with lower levels also detected in the liver, kidneys and lungs while excretion through urine was also reported in an animal model [112]. Oxidative stress and translocation of TiO2 nanoparticles to the brain after injection in the abdominal cavity were reported in a mouse model after 14 days [113]. The results of these animal model studies should be interpreted cautiously as the levels of injected Ti particles are high and may exceed exposure levels caused by dental implants.

In a cadaver study, Ti particles released from dental implants were detectable in jaw bones and bone marrow tissues [114]. The amount of Ti detected was related to the distance from the dental implant with particle sizes ranging from 0.5 microns to 40 microns [114]. In an animal model study, Ti particles after peri-implantitis surgery could be detected in the spleen, liver, lung, kidney, and lymph nodes after 4 months [115]. Particles obtained from implantoplasty of dental implants when implanted in the mandible of rats resulted in detectable Ti levels in the brain, spleen, and liver being higher, and vanadium concentration in the brain being higher than positive control after 30 days of exposure. They also noted multinucleated giant cells and histiocytes in the vicinity of the implanted metal particles [116]. A second animal study reported that when mandibular defects of rats were filled with metal Ti debris, an increase in Ti levels was seen in the brain, liver, lung, and spleen compared to controls [117].

Some studies have found that there is no significant increase in systemic redistribution of Ti ions in instances of peri-implantitis or failures. An animal study found that distant organ Ti levels were low after implant insertion and in the presence of implant failures [118]. Additionally, serum levels in patients with dental implants showed no significant increases in blood metal levels either immediately or up to 12 months after implant placement [119]. In a human study, it was noted that there was no significant increase in metal ions in the blood of patients who had received a dental implant [120]. A translational study also reported that serum levels of trace metal ions were not significantly different between implants with peri-implantitis compared to healthy implants [43]. Based on the available evidence, there appears to be contradicting evidence on the effect of Ti particles on distant organs. Further studies are required to elucidate this response in greater detail.

6. Discussion

The oral environment is complex with several factors like host response, oral microbiome, related pH changes, salivary composition, and temperature that can vary in each niche. Ti is particularly susceptible to local levels of fluoride. The salivary composition of fluoride ions (Fl^-) can be affected by various commercial products like toothpaste and mouth rinses. The Fl^- can react with the hydrogen ion (H^+) leading to the formation of hydrofluoric acid (HF) which is known to have a high affinity to Ti which can accelerate corrosion [121]. This phenomenon of Fl^- induced corrosion of Ti is accelerated in an acidic environment [122,123]. The fluoride concentration can also negatively influence the galvanic reactions between Ti and other alloys like cobalt chromium [124]. The TiO_2 layer is also known to have electrostatic interaction and an ability to adsorb proteins, carbohydrates, mucin, and glycoproteins present from the saliva [121]. Mucin present in the saliva can bind to Calcium ($Ca2^+$) and phosphate ($PO4^-$) ions. These $Ca2^+$ ions interact with the negatively charged protein and form a ligand between TiO_2 surface and the protein [125]. Dental amalgam on the other hand has the potential to suppress Ti release under acidic and basic conditions as reported in an in-vitro testing condition [126]. One additional factor to consider is the type of Ti or Ti alloy being used. While commercially pure titanium (Cp Ti) grade IV is a common material used for dental implants, other alloys such as Ti-Zirconia and Ti6Al4V have been used for dental implant fixtures and implant abutments for prosthetic connections [127–129]. Ti-zirconia alloys have similar biocompatibility to commercially pure Ti [130–133] and commercially pure Ti is known to have higher corrosion resistance than Ti6Al4V but the majority of the evidence supporting this is from in-vitro studies trying to mimic oral conditions [134–136]. Evidence from clinical studies on the different corrosion behaviors of Ti compared to its alloys are lacking.

One factor that is relevant but not often discussed is that the study of Ti levels in oral tissues and fluids through techniques such as inductively coupled plasma mass spectrometry or inductively coupled plasma

optical emission spectrometry requires an increasingly clean environment and sample processing with a focus on maximal reduction of Ti contamination [25]. Ti is present in oral care products, makeup and food [137,138] which could influence the detection of Ti in the oral cavity. In future studies, such confounding factors have to be considered. Additionally, Ti is used as a catalyst for plastic production [139] which adds another a challenge to study it in oral samples where concentrations are low. This is relevant since many of the laboratory techniques [19,25] to study Ti utilize potent acids such as hydrofluoric acid which may potentially leach out Ti from lab equipment. As more refined techniques and protocols are developed, this background contamination can be eliminated to minimize the noise from the results of the clinical and translational studies.

7. Theories on the etiopathogenesis of peri-implantitis

There is unequivocal evidence from pre-clinical studies that Ti particles have a multi-fold effect on the adjacent structures and can elicit a pro-inflammatory effect that favors clinical inflammation and bone resorption through its effect on various cells involved in the process of maintenance of osseointegration including osteoblasts, macrophages, fibroblasts among others [140,141]. Indeed, the World Workshop on Periodontal and Peri-implant Diseases concluded that bacterial plaque was the sole etiological agent in peri-implant mucositis and peri-implantitis similar to periodontitis with some other notable risk factors and risk indicators while stating the lack of studies to substantiate the role of Ti corrosion products on peri-implant inflammation [142]. This viewpoint has been challenged since conventional anti-infective-based therapies lead to unpredictable results for peri-implantitis compared to periodontitis lesions [11,143].

Based on these observations, three theories have been speculated and postulated to explain the etiological process of peri-implantitis. One theory is that conventional bacterial plaque causes inflammation of peri-implant tissues synonymous with periodontitis [142]. A second theory has emerged suggesting that peri-implant inflammation may be a result of "metallosis" or a foreign body reaction of Ti particles and products released from the dental implant [144]. In addition, a third theory exists that unifies these two above-mentioned concepts that there could be a three-way relationship between peri-implant microbiome, the host, and Ti particles and ions [11,140,145] with each factor capable of influencing each other (Fig. 2).

The evidence supporting and refuting the three theories points to the plausibility that a primary foreign body reaction or a primary plaque biofilm-mediated inflammatory process may be at play, independent of each other in a specific site or patient or as a synergistic process depending on the local environment. Since the conditions share common signs and symptoms irrespective of the etiology (bacteria or Ti particles or both), our current diagnostic criteria of increased probing depth, inflammation, and bone loss are unable to differentiate between the three etiologic processes (bacterial plaque-induced or Ti particle-induced or both). Hence, it is possible that what we diagnose and categorize as one condition "peri-implantitis" may be caused by three independent etiologic pathways (bacterial plaque mediated or Ti particle and ion mediated or both) depending on the patient and site-specific factors. This points out the presence of specific "etiological signatures" unique to a patient and implant in the presence of peri-implant inflammation. As of yet, there are no validated clinical tools to differentiate the processes and "etiologic signatures". Further clinical and translational studies are required to establish the processes involved and better clarify the role of Ti particles in the etiopathogenesis of peri-implantitis through one of the theories listed above (Fig. 2). Clinical studies looking at more than one etiological factor that is sufficiently powered to detect the presence of specific "etiological signatures" would be able to shed greater light on the mechanisms outlined above. This is especially relevant as conventional anti-infective therapies for peri-implantitis have a direct detrimental role on the bio-material integrity

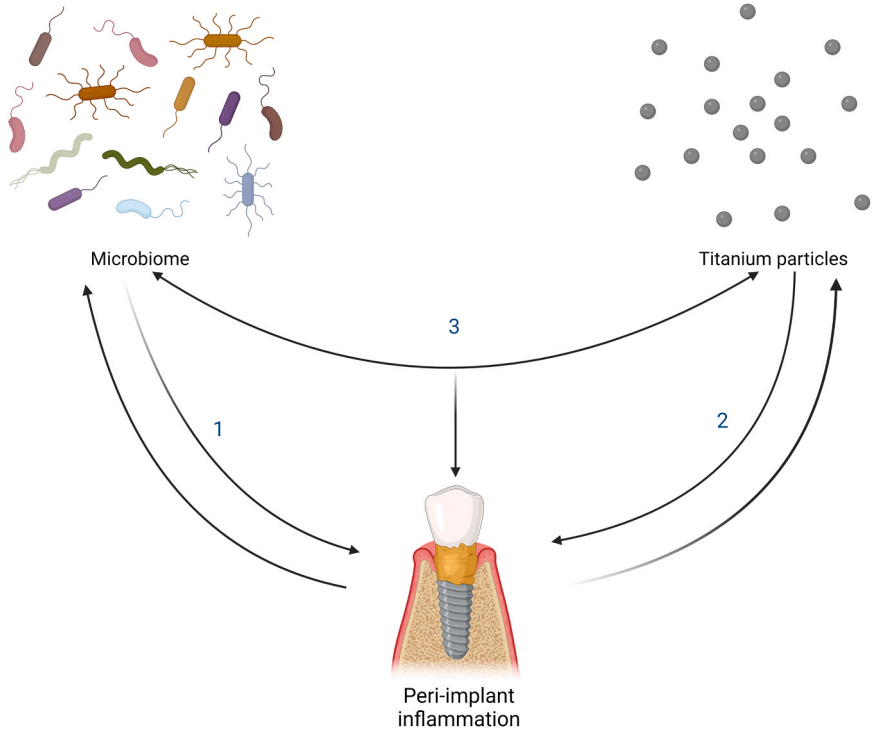

Fig. 2. Fig. 2 is a schematic representation of the possible interaction between the host, dental implant and the microbiome. 1: Microbiome will act on the host tissue causing inflammation and host factors in turn will modulate the microbial colonization; 2: Titanium particles can act on host tissue to modulate inflammation and host response can modulate the titanium corrosion; 3: Titanium particles can affect the microbial composition of the plaque/biofilm, and microbial products and colonization can affect titanium corrosion. These factors are capable of independently or synergistically acting upon the host to induce and sustain peri-implant inflammation based on the unique clinical circumstances of the host (Created with BioRender.com).

and can promote corrosion [21,101], while strategies that are aimed at preserving bio-material integrity and preventing corrosion may not eliminate all of the biofilms from micro-roughened implant surfaces. This is also relevant in cases of peri-implantitis that is refractory to conventional anti-infective therapy where the biocompatibility of the Ti surface could have been affected as a result of treatment. There is also a need for well-designed studies aimed at identifying the systemic fate of these Ti particles that are harbored in the peri-implant tissues. Since this is an emerging field, further studies are expected to deepen our understanding and unravel the molecular and cellular processes involved in the role of Ti in peri-implant inflammation.

8. Conclusion

Ti implants are in a constant state of equilibrium with the host tissues and microbiome surrounding it. Ti particles and ions associated with dental implants can be detected in peri-implant tissues, plaque, and peri-implant crevicular fluid. There is evidence to suggest that these particles can lead the host into a pro-inflammatory state and tissue damage by a direct effect on cells and through the release of pro-inflammatory cytokines. The majority of the evidence reviewed is from in-vitro, animal, and limited human studies. There is a need for further clinical and translational studies to elucidate the role of these particles in peri-implant inflammation pathogenesis and treatment outcomes.

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CRediT authorship contribution statement

Vinayak M Joshi: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Harsha M:** Writing – review & editing, Writing – original draft, Resources. **Eswar Kandaswamy:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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