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REVIEW ARTICLE OPEN

# Titanium particles in peri-implantitis: distribution, pathogenesis and prospects

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Peri-implantitis is one of the most important biological complications in the field of oral implantology. Identifying the causative factors of peri-implant inflammation and osteolysis is crucial for the disease's prevention and treatment. The underlying risk factors and detailed pathogenesis of peri-implantitis remain to be elucidated. Titanium-based implants as the most widely used implant inevitably release titanium particles into the surrounding tissue. Notably, the concentration of titanium particles increases significantly at peri-implantitis sites, suggesting titanium particles as a potential risk factor for the condition. Previous studies have indicated that titanium particles can induce peripheral osteolysis and foster the development of aseptic osteoarthritis in orthopedic joint replacement. However, it remains unconfirmed whether this phenomenon also triggers inflammation and bone resorption in peri-implant tissues. This review summarizes the distribution of titanium particles around the implant, the potential roles in peri-implantitis and the prevalent prevention strategies, which expects to provide new directions for the study of the pathogenesis and treatment of peri-implantitis.

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## INTRODUCTION

Peri-implantitis is a prevalent biological complication in the field of oral implantology, and it is challenging to treat. It is mainly manifested by peri-implant soft tissue inflammation and progressive bone resorption.[1,2] Epidemiological studies have shown that the incidence of peri-implantitis is as high as 20%-47%.[3] Without appropriate treatment, peri-implantitis can lead to poor treatment outcomes and may even require the removal of the implant. Peri-implantitis has seriously affected patient treatment experience and the broader application of implant therapy. There are numerous risk factors that induce peri-implantitis progression. Due to the driving factors, progression process and clinical manifestations of peri-implantitis are similar to periodontitis, current study considers peri-implantitis to be a class of inflammatory diseases, with bacteria as the initiating factor.[4] However, compared with periodontitis, peri-implantitis exhibits a larger area of inflammatory cell infiltration and more rapid and severe bone loss.[5] Bacterial factors alone cannot fully explain the pathological process of peri-implantitis.

Titanium has a long history as an implant material. In the United States, animal experiments on titanium-based implants were conducted as early as 1940, and the first titanium-based dental prostheses were in reported in 1977.[6] Due to their long fatigue life, corrosion resistance, good biocompatibility and low Young's modulus, titanium and its alloys have been extensively used in the field of oral implants.[7] At present, titanium implants are the most widely used commercial dental implants. However, factors such as friction between implant and bone surface, wear caused by biomechanical load, and biological friction corrosion effect inevitably lead to the release of titanium particles in the surrounding tissues.[8] The 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions mentioned some evidence of a link between titanium particles and peri-implantitis, but its role as a risk indicator of peri-implantitis remains to be further determined.[9,10] The role of titanium particles in the progression of peri-implantitis may be underestimated. In the following contents, this article reviews the risk factors influencing the release of titanium particles around the implant, the dispersion of these particles, their potential role in peri-implantitis onset, and possible prevention and treatment methods (Fig. 1). In the first section, we examine the factors impacting the release of titanium particles in the implant's vicinity. We also analyze the changes in titanium particle distribution at peri-implantitis sites, suggesting a possible role in peri-implantitis development. The second section summarizes potential mechanisms through which titanium particles could affect peri-implantitis progression, offering insights for future treatment approaches. The third section evaluates existing treatment strategies. Finally, we summarize and conclude the paper, addressing current limitations and future research directions. This work aims to provide research insights into the role of titanium particles in peri-implantitis and strategies for its prevention and treatment.

## THE RELEASE OF TITANIUM PARTICLES IN THE PERI-IMPLANT ENVIRONMENT

During the process from implantation site preparation to long-term maintenance of implants, titanium particles may overflow. Several studies have detailed this process. For instance, Delgardo-

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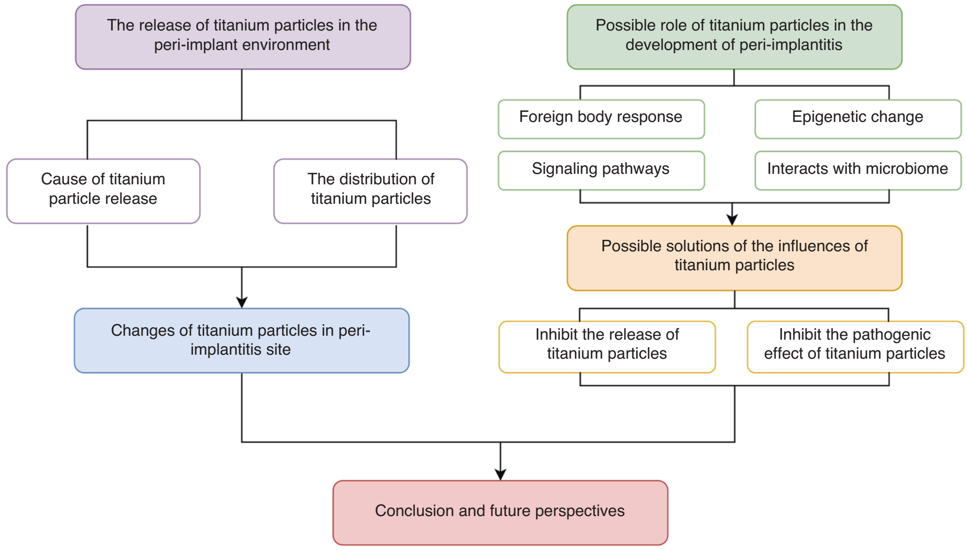


**Fig. 1** The outline of this review. First, we clarified the causes of the release of titanium particles around the implant and the distribution patterns of titanium particles. Then, we analyzed the changes of the distribution of titanium particles at peri-implantitis site, and summarized the possible mechanism of titanium particles in promoting the development of inflammation and existing prevention and treatment strategies. Finally, we conclude and project future research prospects in this field

Ruiz et al. [11] reviewed the causes of the release of titanium particles and titanium ions during implantation surgery, prosthetic stage and maintenance stage, they identified the risk factors such as mechanical factors, bacteria, saliva, micro-space and fluoride. Romanos et al. [12] also observed that titanium particles could be released due to placement, under loading and maintenance factors. Hence, we will further discuss the potential release of titanium particles according to the chronological order of implantation treatment and previous scholarly reviews in order to provide a clear understanding of the cause of the titanium particles release (Fig. 2).

## Cause of titanium particle release around implants

From implant implantation preparation to long-term maintenance, there are many factors that lead to the release of titanium particles around the implant. Friction between drill bit and bone surface and other factors will inevitably lead to the release of titanium particles into the surrounding ground tissues.

*Implant site preparation stage*. Titanium particles are produced during the preparation of the implant site. The most common problems in the process of implant site preparation are wear of the drill bit and heat generation.[13] During the implant bed preparation, the drill bit is generally used with irrigation (this reduces heat generation), but the wear of the drill bit is unavoidable.

The wear of the implant drill produces metal particles. Rashad et al. [14] discovered that the attrition of metal particles occurred during implant site preparation procedure. They compared the effect of several implant system instruments in implant position point preparation. EDS analysis of the water flushed during the operation revealed the presence of Ti, Ag, Cu, Fe, Mn, Zr, Cr and other elements in varying concentrations. Alevizakos et al. [15] noticed signs of wear on the main cutting edges of the implant bit after 60 osteotomies on the pig mandible. By drilling into cattle ribs, Allsobrook et al. [16] determined that drill corrosion is potentially important in determining the life span of implant burs. Natalia et al. [17] found that the depth of drilling was the main factor affecting the temperature change, and no obvious wear was observed after using the drill 50 times. Christian et al. [18] investigated the relationship between drill bits, bone density, and temperature increase through in vitro experiments. They

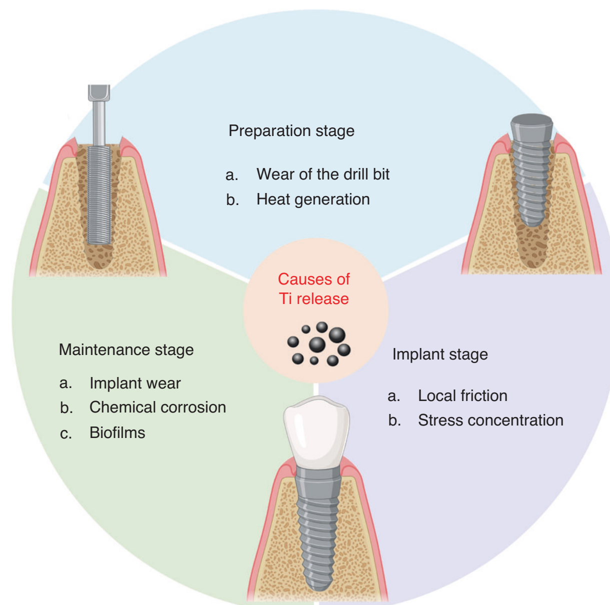


**Fig. 2** The release of titanium particles in the peri-implant environment. In the preparation stage, the wear of the drill bit and the heat generated during the drilling process release some metal particles. In the stage of implantation, the friction between the implant and bone surface, local stress and other factors lead to further release of titanium particles. In the stage of long-term maintenance of the implant, local wear, micro-movement and micro-gap, chemical corrosion and plaque biofilm interaction contribute to the continuous release of titanium particles

discovered that the increased bone density and smaller drill diameter result in a more noticeable temperature rise during surgery, which could significantly affect bone response and drill wear.

Evidence have shown that during the preparation of the implant site, the abrasion of the drill bit against the bone tissue produce metal particles, which may remain around the implant site, therefore replacement used drills may reduce the release of these particles.

*Implant stage*. After the implant was implanted, numerous studies instantaneously detected the presence of titanium particles around the implant. Furranchi et al. [8] implanted titanium-based implants in the femur and tibia of sheep to investigate the shedding of titanium fragments from the implant's surface during initial healing stage. They discovered titanium particles, ranging from 3 to 60 μm in size in peri-implant tissues immediately post-surgery. Barrak et al. [19] placed implants in the mandible of pigs and found that metal particles could be detected in the tissue surrounding the implant after implantation immediately. They also found that the larger the diameter of the implant, the more metal particles were released. Additionally, cylindrical implants released more metal particles than conical implants. Guan et al. [20] simulated the mechanical changes during implant implantation and discovered areas of stress concentration around the implant. These areas were potential sites for the generation and release into the bone tissue.

The appearance of titanium particles immediately after implant placement, predominantly caused by local friction and stress concentration, seems unavoidable at present. We can only hope that future advancements in implant materials and surgical procedure optimization will alter this phenomenon.

*Long-term maintenance stage*. Titanium particles remain in the tissue surrounding the implant during long-term maintenance after implantation. In the late stage of implant implantation, titanium particles will be released into the surrounding tissues due to chemical corrosion, micro-gap and micromovement, and other reasons

Implant wear: Micromotions and fretting damage at the implant/bone interface are overlooked due to limitations in inspection methods, but it is particularly important for the long-term existence of the implant.[21] The micro-gap and micro-movement between the implant and the upper crown connection, the conventional mechanical cleaning of the implant, and the destruction of the titanium oxide protective layer will promote the increase of implant wear and eventually lead to the gradual release of titanium particles from the implant to the surrounding tissues. The micro-gap and micro-movement between the implant and abutment are caused by the production error of the implant, masticatory load and other reasons, leading directly or indirectly to microleakage and mechanical wear.[12,22] Patricia A Lopes et al. found small defects ranging from 0.5 to 5.6 μm on different regions of the abutment surface. These defects resulted in the micro-gap in the connection between the implant and the abutment, affecting the adaptability of the implant and the abutment.[23] Kai Blum et al. applied a force of 98 N to various implants and abutments for 100 000, 200 000, and 1 million cycles, respectively. They found micro-gap between the implants and abutments, with gap size increasing with cyclic loading. All implants showed wear regardless of the interface design.[24] In addition, micromotion between the implant and abutment will be generated under the action of chewing force, further increasing the micro-gap between the implant and abutment components, which will lead to microleakage, material wear, titanium particle release, and screw loosening.[25–27] The friction caused by micromotion can also damage the oxide layer on the surface of the titanium-based implant, leading to the release of titanium particles. When the titanium implant is exposed to the air, a layer of oxide film will form on the implant surface. This improves the implant's corrosion resistance and provides good biocompatibility, promoting wound healing and cell growth at the implant site.[28–30] However, wear of the implant can destroy the oxide film and exposure the underlying metal, making it more susceptible to corrosion and releasing titanium particles and titanium ions.[31]

Micro-gap and micro-motion are inevitable. Clinicians should aim to choose the implant system with smaller micro-gap, and implant manufacturers should provide relevant data to allow clinicians to make a more informed choice.

In addition, Alrabeah et al. [32] analyzed the effects of platform-matched and platform-switched implants on metal particle and ion release levels. They found that titanium had the highest release rate due to corrosion, irrespective of the substrate size or connection mode. The daily maintenance of the implant and prevention and treatment of implant related diseases can also contribute to increased implant wear, eventually leading to the release of titanium particles. Prevention and treatment of peri-implant mucositis and peri-implantitis involve cleaning the implant surface exposed to the oral environment using mechanical and chemical methods. This process generates a significant amount of tiny titanium particles into the surrounding tissue.[33] During implant decontamination, metal scrapers and ultrasound can effectively remove plaque biofilm, but also cause the release of titanium particles from titanium implants.[34] Anna Louropoulou et al. evaluated the effects of various instruments on titanium surfaces and found that non-metallic instruments caused less damage to smooth and rough titanium surfaces. Metallic instruments can cause severe damage to the smooth titanium surface, while non-metallic instruments cause less damage.[35] Valerie Ronay et al. evaluated the cleaning efficiency of commonly used implant debridement methods by simulating non-surgical treatment of peri-implantitis in vitro, SEM results showed that the morphology of titanium surface changed significantly after scaling and ultrasonic treatment.[36]

These findings suggest that clinicians should consider not only the effect of implant decontamination and inflammation resolution in the daily maintenance and prevention of implant-related diseases post-implantation, but also the impact of treatment methods on the implant's condition. Improper treatment can cause further damage to the implant, release more titanium particles, and potentially lead to peri-implant diseases.

Chemical corrosion: Chemical corrosion is also an important cause of titanium particle leakage. Mechanical wear causes damage to the oxide layer of the implant surface, making the implant more susceptible to corrosion. In addition, the complex environment in the oral cavity, including constant changes in temperature, PH, bacteria and other components, and exposure to various chemical agents such as fluoride toothpaste, increase the risk of implant corrosion, resulting in the release of titanium into the environment around the implant in forms such as particles and ions.[37,38]

Sutton E Wheelis et al. discovered that an acidic environment and friction could significantly alter the surface roughness of titanium and promote its corrosion.[39] Chen et al. found that under fluoride ion conditions, the titanium oxide film barrier was destroyed and the corrosion resistance of pure titanium decreased with increasing fluoride concentration. The sensitivity to corrosion of pure titanium increased after exposure to high fluoride concentration, thereby accelerating the release of titanium ions. This effect was even more pronounced in acidic environments.[40] Chen et al. studied Ti-6Al-4V dental implants and found that its corrosion and by-products were significant causes of bone loss around implants. This corrosion effect was exacerbated in a fluorine-rich environment.[41] Barbieri et al. immersed implants with different surface treatments in human saliva and detected that titanium began to be released from all implant surfaces after seven days, with the release increasing over a period of six months.[42] Leonardo P Faverani et al. studied the effects of carbamide peroxide, hydrogen peroxide, and cola beverage on the surface morphology of commercially pure titanium (CP-Ti) and Ti-6Al-4V, and found that the surface morphology of CP-Ti exposed to 35% hydrogen peroxide changed significantly.[43] Oral pathogens can adhere to and colonize the titanium surface, leading to its corrosion and degradation.[44] The titanium particles and titanium ions produced after corrosion of titanium implants can further aggravate the corrosion process. Alhamad et al. found that high concentrations of titanium in saliva can increase the corrosion rate of titanium implants, posing a potential risk of increased implant associated adverse tissue reactions.[45]

Based on current research, there is a mutually reinforcing relationship between the chemical corrosion of implants and the release of titanium particles. Implant corrosion may result in the release of titanium particles. The increased concentration of titanium around the implant can create a more corrosive external environment. Moreover, under inflammatory conditions, the corrosion sensitivity of the implant escalates, an issue that can be mitigated by altering the surface microstructure of the implant.[46] However, the corrosion of implants, the release of titanium particles and the emergence of inflammation all have mutual reinforcing effects. Determining the initiating factor and the mechanism of the entire process requires further research.

Biofilms: Contrary to titanium-based prostheses in large joint arthroplasty, dental implants are exposed to the complex oral microenvironment. Bacteria adhering to the implant surface can easily form biofilms which can influence the implant in various ways.

Sridhar et al. inserted implants in bacterial culture medium and observed that the acidity of the media promoted implant corrosion causing discoloration, roughness, pitting and severe surface rust.[47] Mathew et al. discovered that lipopolysaccharide (LPS) in bacteria accelerated the exchange between titanium ions and saliva, which diminished the corrosion resistance of titanium and increased its surface roughness.[48] The bacteria on the implant surface not only trigger an inflammatory immune response, but also initiate electrochemical changes on the titanium surface, specifically corrosion, which aggravates the inflammatory response. Safioti et al. also found higher titanium concentrations in plaque from tissues surrounding peri-implantitis.[49] The titanium dioxide's electrostatic force and ionic bond on the implant surface can attract bacterial adsorption. The interaction between the metal surface and the oral environment could lead to the release of implant degradation products into the peri-implant environment, thereby increasing the environmental stress of the microbial community.[1]

Given that bacterial biofilms on the implant surface can cause a series of adverse effects, various methods are employed for implant surface decontamination during daily maintenance. However, these actions could also harm the implant itself and lead to the release of titanium particles. Techniques such as mechanical removal, laser treatment, photodynamic therapy, air polishing, ultrasonic treatment, chemotherapy, electrochemical therapy and the use of antibacterial drugs effectively remove bacterial biofilms. However, these methods could also negatively impact the implant, which could be considered a form of implant wear to a certain extent.[34]

The bacterial biofilm on the implant surface can promote the release of titanium particles and contribute to the development of peri-implantitis. Currently, no uniform standard exists for the removal of bacterial biofilms, a process which could inadvertently damage the implant. Therefore, the optimization of implant decontamination methods and the establishment of uniform standards are essential areas for future research.

Numerous factors can cause the release of titanium particles from the implant, from the preparation stage prior to implantation to the long-term maintenance post-implantation. The wear and tear of implants, chemical corrosion, bacterial biofilm and other factors on the implant surface can all result in surface damage. These factors rarely exist in isolation; instead, they interact, complicating the study of preventative strategies for the release of titanium particles around implants. Furthermore, the titanium particles released from implants have significant effects on peri-implant tissues. They are closely associated with the progression of peri-implantitis and other related diseases. As such, this topic warrants increased attention.

The distribution of titanium particles

The release of titanium particles is inevitable during implant treatment. Metal particles of different sizes are scattered in the tissue around the implant. Understanding the distribution and location of titanium particles released from implants is crucial for comprehending their role in t implant-related diseases.

Studies indicate that titanium particles are primarily found around implants, epithelial cells, connective tissue, macrophages, and inside bone.[50] Flatebø et al. [51] analyzed the mucosal tissue around the implant six months after implantation, discovering a significant increase in the concentration of titanium particles in the adjacent oral mucosal epithelial tissue. Similarly, He et al. [52] investigated the release of titanium particles from human mandibular implants and found that the intensity of titanium increased with distance from the implant, specifically between 556 and 1 587 μm. They also discovered particles ranging from 0.5 to 40 μm in size in human mandibular bone marrow tissue 60 to 700 μm away from the implant. In addition, titanium particles were found in the peri-implant soft tissues, submucosal plaques, and distant lymph nodes.[53] They can also be transferred systemically through blood supply. Ann Wennerberg et al. implanted implants in rats and traced nanoparticles on the implant surface, and these particles could be detected in blood, liver and other parts.[54] Research shows that titanium particles can diffuse through the plasma proteins or macrophages in the blood, eventually reaching the lung, spleen, liver or distant lymph nodes.[55] Conversely, Guglielmotti et al. injected a solution containing $TiO_2$ particles into the abdominal cavity of rats, micron-sized titanium particles were detected in the gingiva, suggesting that titanium from other parts of the body can also reach the gingiva through specific pathways.[56]

Titanium particles released from implants can be disseminated throughout the body. However, the potential systemic diseases this phenomenon may cause remain uncertain.. In the tissues surrounding implants, titanium particles can be found in alveolar bone, gingiva, macrophages, etc., which must be considered when studying the progression of implant-related diseases such as peri-implantitis. Despite their presence in the environment around dental implants, the role of titanium particles in the development of peri-implantitis.

## CHANGES OF TITANIUM PARTICLES IN PERI-IMPLANTITIS SITE

Existing studies confirm the release of titanium particles into the surrounding tissues from titanium implants, but the impact of these titanium particles on the development of peri-implantitis is still a contentious issue. The following article will analyze the distribution of titanium particles in the peri-implant tissues in patients with peri-implantitis. By identifying the differences, we aim to uncover the potential relationship between titanium particles and the progression of peri-implantitis.

To explore the distribution changes in titanium particles at the site of peri-implantitis, we used 'peri-implantitis' and 'titanium particles' as search keywords in PubMed database. Our survey of the existing studies (Table 1) revealed that all investigations detected titanium particles at the peri-implantitis site, primarily within the gingival tissue around the implant. Additional findings highlighted the presence of titanium particles in the alveolar bone tissue,[57] gingival tissue,[58]mucosae tissue[57,59] and deeper implant site.[60] Some studies used tissue samples from patients with periodontitis[58,61] as controls, while others utilized tissue from healthy implants[49,59,60] for comparison. Prior reviews have shown no significant difference between the distribution of titanium particles in patients with peri-implantitis and healthy individuals.

**Table 1.** Relevant study on the correlation of titanium particles at the peri-implantitis sites: Compared with periodontitis patients and the tissues around healthy implants, the concentration of titanium particles at the site of peri-implantitis was significantly higher, and the titanium particles were distributed in the gingival, mucous membrane, bone and other tissues around the implant, with different concentrations and sizes

| Study | Number of patients | Detection method | Ti concentration | | Ti particle size | Ti particle location |
|---|---|---|---|---|---|---|
| | | | Peri-implantitis | Control | | |
| Pettersson et al. [58] | 13 peri-implantitis and 11 periodontitis patients | LM、SEM、TEM | $(98.7 \pm 85.6)\ \mu g \cdot g^{-1}$ | $(1.2 \pm 0.9)\ \mu g \cdot g^{-1}$ | $(10.9 \pm 35.7)\ \mu m^2$ | Gingival tissue around Ti implant |
| Mia Rakic et al. [61] | 39 peri-implantitis cases and 35 periodontitis as control | LM、H&E Staining、dispersive X-ray spectrometry | / | / | $(8.9 \pm 24.8)\ \mu m^2$ | Free inter-cellular content in peri-implant tissue |
| Fretwurst et al. [57] | 12 peri-implantitis patients' biopsies | LM、radiation X-ray fluorescence spectroscopy | $3 \times 10^5$in bone $7 \times 10^5$in soft tissue (area scan) | / | / | Seven bone samples, five mucosal samples |
| Daubert et al. [60] | 21 peri-implantitis and 24 healthy implants | ICP-MS | $(0.2 \pm 0.6/0.5)$ ng sample | $(0.1 \pm 0.2/0.5)$ ng sample | / | Deepest site for each included implant |
| Wilson Jr et al. [125] | 36 peri-implantitis patients' biopsies | LM、SEM | 0.6% titanium element in samples | / | 9-54 μm | Peri-implant tissue, Ti was surrounded by inflammatory cell |
| Pettersson et al. [126] | 3 peri-implantitis patients' biopsies | ICP-MS | 7.3 to 38.9 $\mu mol \cdot L^{-1}$ | / | / | Peri-implant gingiva |
| Safioti et al. [49] | Submucosal plaque from 20 implants with peri-implantitis and 20 healthy implants | ICP-MS | $0.85 \pm 2.47$ | $0.07 \pm 0.19$ | 48.73 $ng \cdot \mu L^{-1}$ | Submucosal plaque from implants |
| Olmedo et al. [59] | 15 peri-implantitis and 15 healthy implants | LM、ICP-MS | $2.02 \times 10^{-9}$-$2.44 \times 10^{-9}$ | $0.41 \times 10^{-9}$-$0.88 \times 10^{-9}$ | | Mucosae with and without peri-implantitis |
| Nelson et al. [127] | patients who had either titanium implants exhibiting severe peri-implantitis | μ-XRF、 Nano-XRF | / | / | several micrometers to 100 nm | Soft tissue biopsies |
| Berryman et al. [128] | 10 peri-implantitis patients tissue biopsies | SEM-EDS | titanium wear particles in 90% of the samples | / | / | Peri-implant tissue |

Nevertheless, significant variations were observed in the size and concentration of titanium particles detected across different experiments. It was consistently found that the concentration of titanium particles was significantly higher at the site of peri-implantitis. In contrast, the sources of titanium particles in periodontitis patients were significantly less than those in peri-implant patients due to the absence of titanium-based implants. This discrepancy suggests that titanium particle distribution data obtained from some studies might not reflect the situation accurately at the inflamed sites around the implant. Therefore, these results still warrant further discussion.. While we observed that only a limited number of studies used tissues from around healthy implants as control groups for comparison, many studies merely collected tissues from around inflammatory sites of implants to analyzed the distribution of titanium particles. This may be attributed to the challenges in acquiring tissues from around healthy implants in clinical work and the difficulty in gathering an adequate sample size for comparative study. For future research, it is recommended that some gingival tissue can be collected during the second surgery in the course of implantation treatment. Alternatively, part of the surrounding tissue of the implant can be collected during the surgical removal of implants due to non-inflammatory reasons. This would allow the analysis of the patten of titanium particle release after standard implant procedures, enhancing our understanding of the role of titanium particles in the process of peri-implantitis.

Many studies have primarily focused on examining the size, concentration and location of titanium particles around the implant. Results consistently show a significantly higher concentration of titanium particles at the inflammatory site around the implant compared to normal sites. However, t findings vary greatly across different studies concerning particle concentration, distribution location and size. This variability may result from the broad distribution of titanium particles and the differences in the sample location and size across research groups. It may also be related to variation in peri-implantitis severity among individuals. Complicating matters further, the lack of standardized measurement process leads different research teams to adopt varying standards for assessing the distribution of titanium particles at the peri-implantitis site. Some studies measure titanium particle concentrations, while others detect titanium element content. The use of different detection methods and measurement units impedes the comparison outcomes, making it challenging to explore the role of titanium particles in the development of peri-implantitis. Future research should consider establishing unified standard for the detection of titanium particles around the implant, including stipulations on samples collection range and the categorization of collected gingival, mucous membrane and bone tissue etc. In addition, the time of implant function, clinical manifestations and the differences between patients themselves should also be taken into account. Standardized sampling will greatly help to study the mechanism of action of titanium particles in the development of peri-implantitis.

In conclusion, due to the disparities in the research results on titanium particles and the insufficiency of sample size, it is challenging to explore the role of titanium particles in the development of peri-implantitis. It remains difficult to determine how titanium particles contributes to peri-implantitis, understand the governing laws, identify the effective concentration and size, and locate where the distribution of these particles is impactful. These lingering questions necessitate future exploration. In the subsequent section, we will review the extant literature on the role of titanium particles in the progression of peri-implantitis and summarize the potential influences, hoping to offering insights for further study of the role of titanium particles in the progression of peri-implantitis.

## POSSIBLE ROLE OF TITANIUM PARTICLES IN THE DEVELOPMENT OF PERI-IMPLANTITIS

While the current research on the impact of titanium particles on the development of peri-implantitis remains contentious, a large number of scholars have investigated the potential role of titanium particles. Many studies highlight the inflammatory effect of titanium particles. Furthermore, titanium particles produced by wear and tear after artificial joint replacement can cause chronic inflammation. In the following part, we will summarize the potential ways in which various forms of titanium particles can influence the development of peri-implantitis, and tried to provide new directions for subsequent research (Fig. 3).

### Foreign body response

Foreign body reaction refers to the response of macrophages and allogeneic giant cells to inflammation and wound healing following the implantation of medical devices, prostheses or biomaterials.[62] Many scholars argue that titanium particles as a foreign particle, like other metal particles, instigate a foreign body reaction in the host, thus promoting inflammation. They do not suggest a specific role for titanium itself.

The submicron and nanoscale fragments released through the degradation of dental implants are perceived as t foreign bodies that trigger the human immune system, thereby inducing an immune response. Studies have shown that the high concentration of titanium particles at the nanoscale can amplify the inflammatory response of surrounding cells.[63] Macrophages are critical to foreign body reactions as they are precursors to the multinuclear giant cells, a key feature of the condition. The polarization of macrophages affects the entire stage of inflammatory development.[64] In vitro experiments suggest that titanium ions or particles might have toxic or pro-inflammatory effects, and the introduction of titanium particles can instigate M1 type polarization of macrophages, heighten the expressions of inflammation related genes TNF-α, IL-1β, IL-6, RANKL and induce bone loss during bone integration in mouse models.[65] Ege et al. [66] also confirmed that when titanium particles exist as foreign bodies, they are absorbed by macrophages, which then release pro-inflammatory cytokines, IL-1β and IL-6 and TNF-α. These cytokines promote the development of inflammation, potentially leading to osteolysis. Titanium nanoparticles in living organisms can form biological complexes rich in calcium and phosphate, as well as the crystal structure of some hydroxyapatite. When further internalized by osteoblasts, these particles can induce DNA damage.[67] However, other studies collecting peri-implantitis samples found no TPS-phagocytic macrophages or multinuclear giant cells, providing no direct evidence of foreign body reaction induced by titanium particles.[61]

Overall, there is much uncertainty surrounding the concept of foreign body reaction. First of all, titanium implants experience normal wear, and the presence of foreign particles can also be detected in tissue samples around many healthy implants. The simplistic view of foreign body reaction cannot adequately explain why these particles do not induce inflammation. Secondly, although titanium and titanium oxides, silver, zinc oxides and other particles can induce inflammation, the effect vary, and some particles can cause DNA damage, which is closely related to the size of the particles. More evidence is needed to support the idea that titanium particles influence the development of peri-implantitis through foreign body reactions.

### Epigenetic change

Epigenetic changes are closely related to the development of inflammatory diseases, and numerous studies have demonstrated that titanium particles can induce epigenetic changes. The main effect of titanium particles on the development of inflammation is DNA methylation.

Daubert et al. [60] found a rise in DNA cytosine-5MC methylation level in patients with peri-implantitis, and the methylation level

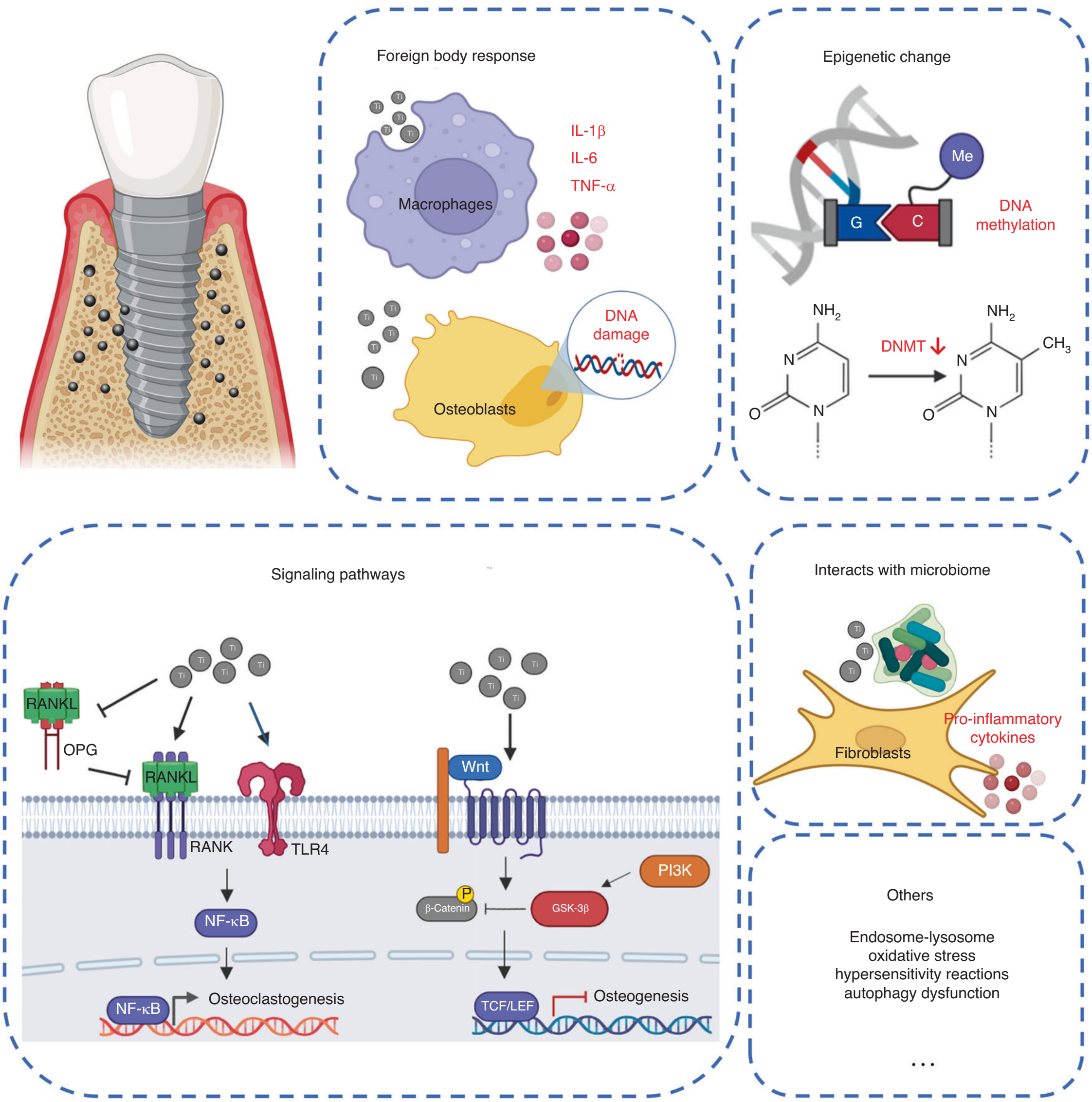


**Fig. 3** Possible role of titanium particles in the development of inflammation. Foreign body reaction: The presence of titanium particles can induce body foreign body reaction, macrophages phagocytize titanium particles, polarize to M1 type, release pro-inflammatory factors, and induce cell DNA damage; Epigenetics: Titanium and titanium oxides can affect the methylation level of cellular DNA cytosine-5MC by regulating the expression of DNA Class A transferase (DNMT), and subsequently affect the inflammatory response; Signaling pathway: Titanium particles can affect the development of inflammation through a variety of signaling pathways, and regulate NF-κB signaling pathway to affect inflammation by regulating the ratio of RANKL/OPG and affecting the expression of TLR protein family. Wnt/β-catenin signaling pathway is a negative feedback regulatory pathway of titanium-induced inflammation, which can inhibit the NLRP3 inflammasome induced by titanium particles, inhibit inflammation and osteolysis. microbiome: Bacterial corrosion can promote the release of titanium particles, and the combined stimulation of titanium particles and bacteria can promote the expression of inflammation in the tissues around the implant. Others: Oxidative stress, autophagy and other factors may also contribute to the inflammation induced by titanium particles

was positively correlated with the concentration of titanium particles, suggesting that DNA methylation may be affected by titanium dissolved products, thereby affecting the development of peri-implantitis. In contrast, Lu et al. [68] found that exposing monocytes (THP-1) to $TiO_2$ or CuO nanoparticles led to a significant downregulation of DNA methyltransferase (DNMT), reducing DNA methylation expression in a dose-dependent manner. Studies demonstrated that $TiO_2$ nanoparticles can induce dose-dependent DNA hypomethylation in peripheral blood monocytes at non-toxic concentrations.[69] Other studies analyzed the correlation between miRNA changes induced by titanium, silver, zinc and oxides and mRNA expression across all metal types, showing that the genes with the most highly correlated genes were those related to cell cycle regulation, inflammatory response and response to metal ions.[70] Furthermore, studies have shown that smooth and moderately rough titanium surfaces have distinct impacts on epigenetic changes.[71] Numerous studies have investigated titanium-induced epigenetic changes, but the conclusions remain inconsistent.[72]

In general, epigenetic changes are likely to be triggered by metal nanoparticles rather than being specific to titanium. Moreover, the difference of titanium particle size and titanium oxide may have different effects on DNA methylation, adding complexity to the study of titanium particle's potential contribution to the development of peri-implantitis through epigenetic effects. From the previous research, we know that nanometer to micron-level titanium particles and $TiO_2$ are present around the implant, necessitating further investigation in this field.

### Signaling pathways

Few studies have delved into changes in signaling pathways involved in the development of peri-implantitis due to titanium particles. Considering the pathogenic role of wear titanium particles after large joint replacement, we have reviewed the signaling pathways that may be influenced by titanium particles, thereby promoting the inflammation development.

*NF-κB / RANKL/OPG Signaling pathway*. Nuclear factor kappa-B (NF-κB) plays a crucial role in cellular responses to external stimuli, which include cytokines, radiation, heavy metals, viruses, etc. This factor is integral to the process of cellular inflammation and immune response. The receptor activator of nuclear factor-kappa B ligand (RANKL) is a NF-κB activated receptor ligand. Osteoprotegerin (OPG) acts as a decoy receptor homolog of RANKL, inhibiting RANK by binding RANKL, and as such, is intimately involved in the regulation of NF-κB signaling pathway.[73,74]

Titanium and titanium oxides promote osteoclast activation and the development of chronic inflammation by activating NF-κB signaling pathway. These substances may even influence other body parts and contribute towards the onset of allergic bronchitis and cardiac inflammation.[75–78]Takanori Wachi et al. [79] found that under LPS stimulation, titanium ions synergistically increased the expression of cytokine CCL2 and RANKL/OPG ratio in gingival tissue. In addition, titanium ion alone elevated the expression of Toll-like receptor 4 (TLR-4) in the gingival epithelium, potentially increasing the sensitivity of gingival epithelium to microorganisms in the oral environment. Studies have analyzed the transcriptomics and proteomics of relevant samples, and confirmed that alterations in biological processes, such as immune/inflammatory or stress responses and TLR signaling pathways are associated with titanium.[72] TLR4 promotes alveolar bone absorption by regulating RANKL/OPG expression ratio and differential inflammatory cytokine production.

The NF-κB/RANKL/OPG Signal pathway significantly influences the activation of osteoclasts and inflammation development, and is the primary focus in the study of inflammation induced by titanium particles.

*Wnt/β-catenin Signaling pathway*. The Wnt-secreted protein family regulates cell growth, differentiation, function and death, and plays an important role in the process of osseointegration.[80] Typical β-catenin-dependent signaling leads to activation of T cell factor/lymphocyte-enhancing factor (TCF/LEF). Macrophages use a molecular mechanism for Wnt signaling that modifies their activity, cytokine production and phagocytosis.[81] The classical Wnt signaling pathway can restrict proinflammatory overactivation via pathogen-associated molecular patterns.[82] Abaricia et al. [83] studied Ti surface-cultured macrophages and found that the mRNA of Wnt ligand was up-regulated in a surface-modified dependent manner. Macrophages serve as an essential source of Wnt ligands during inflammation and healing. Activation of the Wnt/β-catenin signaling pathway can prevent osteolysis induced by titanium particles and shield the damage of osteoblastogenesis.[84,85] Zichuan et al. [86] found that melatonin can regulate the balance between receptor activator of nuclear factor kappa-B ligand and osteoprotegerin through activating Wnt/β-catenin signaling pathway to inhibit the osteolysis induced by titanium particles. The upregulation of Sirtuin 3 can suppress the NLRP3 inflammasome induced by titanium particles through the GSK-3β/β-catenin signaling pathway and promote osteogenesis.[87] Phosphorylation of GSK-3β lessens the degradation of β-catenin and facilitates the translocation of β-catenin from cytoplasm to nucleus, mitigating the inhibitory effect of titanium particles on osteogenesis.[88]

The Wnt/β-catenin signaling pathway is mainly connected with the osteogenesis process, and can targeted to inhibit the inflammation and osteolysis induced by titanium particles in future studies. In aseptic large joint inflammation, previous studies have attempted to inhibit the development of inflammation induced by wear particles by regulating the Wnt/β-catenin signaling pathway. This method could be a potential treatment for peri-implantitis, pending further research confirmation.

*Other signaling pathways*. The phosphatidylinositol 3-kinase (PI3K)/AKT/ Rapamycin (mTOR) signaling pathway plays a significant role in regulating cell survival, proliferation, growth, metabolism, angiogenesis and metastasis.[89] In large joint replacement, PI3K/Akt pathway is one of the signal transduction pathways that mediates the activation of macrophages by wear particles. Inhibiting the expression of PI3K can decrease the activity of alkaline phosphatase (ALP), the expression of osteogenic protein Runx2 on titanium surface, thereby affecting osteogenic ability.[90] Furthermore, inhibition of p110δ, a member of PI3Ks family, can significantly inhibit the expression of TNF-α and IL-6, both associated with inflammation induced by titanium particles.[91] Xian et al. [92] found that titanium particles could promote macrophages autophagy and induce apoptosis through PI3K/Akt signaling pathway. Melatonin can activate butyrate/GPR109A signaling pathway to slow down inflammation and osteolysis. It does this by inducing butyrate enrichment, which activate its receptor GPR109A, inhibiting the activation of NLRP3 inflammasome induced by titanium particles.[93] Additionally, Crocin induces M2 polarization of macrophages by inhibiting p38 MAPK signaling pathway, thereby inhibiting titanium-induced inflammation.[94]

In conclusion, numerous studies have explored the mechanism of titanium particle-induced inflammation and osteolysis, leading to the development of potential therapeutic drugs targeting these signaling pathways. However, these studies mostly focus on the inflammation induced by titanium wear particles after orthopedic implant surgery. Whether the therapeutic methods identified can be applied to peri-implantitis requires further investigation.

### Interacts with microbiome

As a recognized initiating factor of peri-implantitis, titanium particles may interact with the changed bacterial environment around the implant, promoting the development of peri-implantitis. Studies suggest that titanium corrodes in the presence of bacteria in clinical practice.[95] Many studies have explored the interaction of titanium particles with bacteria.

Diane et al. [96] analyzed the bacterial composition and the distribution of titanium particles deep within peri-implantitis sites. They found that peri-implantitis was associated with a significant increase in Veillonella. Large amounts of dissolved titanium were found at 40% of the sample sites, suggesting a connection between the presence of titanium and peri-implant disease status. Irshad Muhammad et al. [97] found that the combined stimulation of titanium wear particles and Pseudomonas gingivalis could promote the expression of genes related to inflammation in peri-implant granulation tissue fibroblasts, thus advancing the development of peri-implantitis. Under bacteria corrosion, the release of titanium particles and ions on the surface of titanium increases,[98] suggesting a mutual promotion between the two. However, contrasting research shows that nanoparticles can inhibit bacterial activities by disrupting the integrity of bacterial cell membranes, inducing oxidative stress responses, causing protein and DNA damage, and inhibiting DNA replication by binding to DNA.[99] This conflicting impact makes studying the interaction between bacteria and titanium particles complex.

Some studies have evaluated the characteristics of bacterial growth on the titanium implant surface and its corrosion effect on the implant, but little is known about the infiltration and accumulation of metal particles in the biofilm surrounding the implant and their possible forms of action.[100] All of this indicates the interaction between bacteria and titanium particles still requires significant exploration.

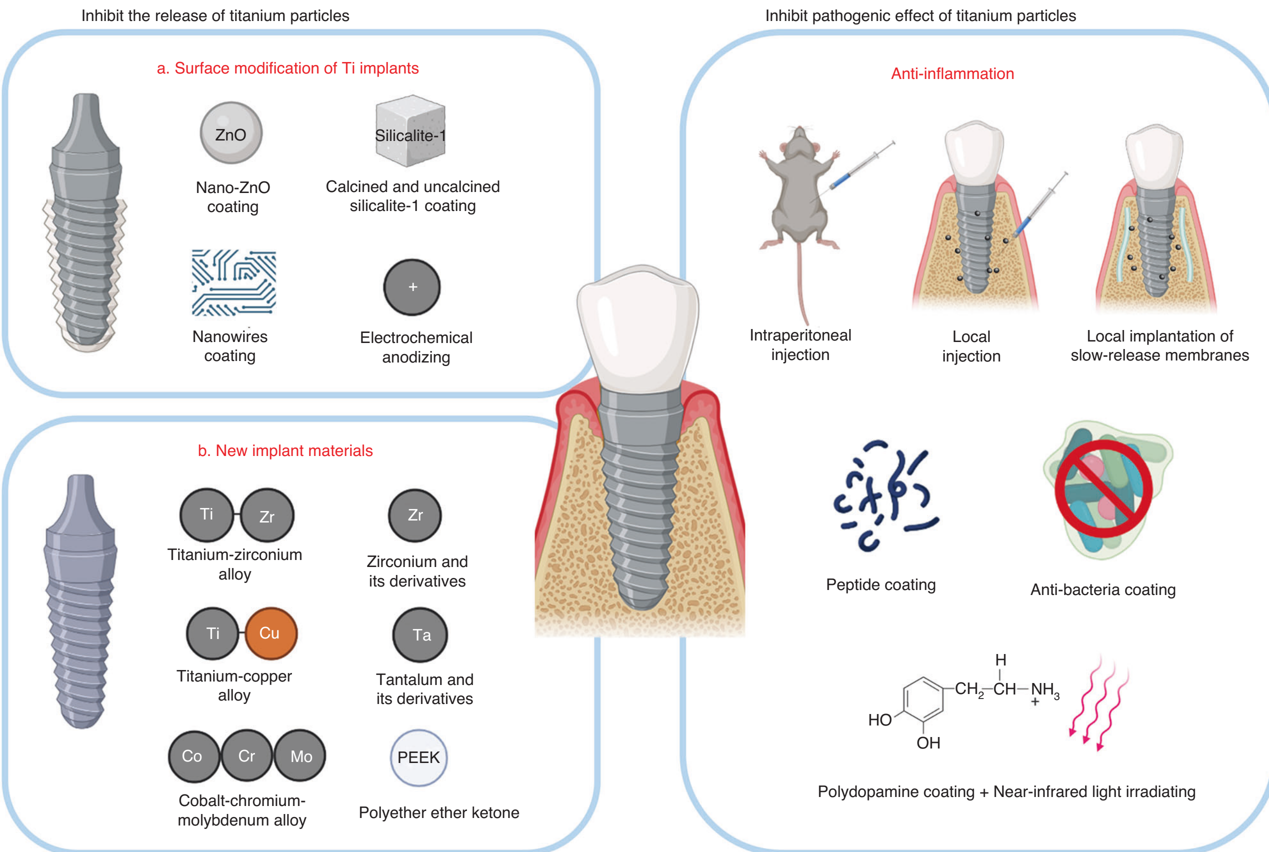


**Fig. 4** Possible solutions of the influence of titanium particles. Inhibit the release of titanium particles: the implant surface is modified by electrospinning, alkali thermal method and other technologies, so that the implant shows a coating film to inhibit the release of titanium particles; Use titanium zirconium, titanium copper and other alloy implants, improve implant materials, zirconium, tantalum, cobalt, chromium, molybdenum and other metal implants and PEEK composite polymer material implants; Inhibition of proinflammatory effect of titanium particles: by indicating modified loaded antibacterial and anti-inflammatory drugs, local injection, local placement of biofilm and other methods

### Others

Several studies suggest that titanium particles may influence the development of peri-implantitis from lesser-explored perspectives. Martin et al. [101] investigated the specific gene expression of inflammatory diseases around oral implants and found that titanium particles may promote the inflammation by activating endosome-lysosome and oxidative stress pathways. Furthermore, the release of titanium particles by implants could potentially enhance antibiotic resistance by altering the microenvironment around the implants. Fernando Suarez-Lopez Del Amo et al. [102] found that Ti particles can activate CHK2, trigger BRCA1 recruitment in oral epithelial cells, and activate DNA damage response (DDR) in epithelial cells. Some studies also propose that titanium and its oxides might bind to proteins, leading to hypersensitivity reactions such as itching, redness, and swelling of the skin. However, the connection between this and the development of inflammation necessitates further clarification.[103] Autophagy is a conserved intracellular self-digestion system. In the large joint inflammation model, wear particles can cause abnormal cellular autophagic activity and autophagy dysfunction, promoting inflammation,[92,104–106] indicating a potential role of autophagy in the development of peri-implantitis.

In summary, the influence of titanium particles on peri-implantitis seems to be multifaceted, involving a variety of interacting factors. This complexity should not be overlooked in future studies. Additionally, a substantial body of studies indicates that titanium particles play a very important role in the development of inflammation, making this an area ripe for further exploration.

## POSSIBLE SOLUTIONS

The previous section aimed to summarize the role of titanium particles in the development of peri-implantitis, and provided an overview of current preventative methods and treatments. By understanding the pathogenic mechanism of titanium particles, we aim to propose potential methods, hoping to offer a new strategy for the prevention and treatment of peri-implantitis. Current strategies mainly focus on mitigating the release of titanium particles and inhibit their pathogenic effect. Many studies have achieved these goals through implant modification and the implementation of various factors. These methods may achieve both objectives simultaneously. In this review, to offer a more lucid perspective on potential treatment for titanium particle-induced peri-implantitis, we will discuss these two aspects separately, hoping to provide a clear direction on future treatment strategies (Fig. 4).

### Inhibit the release of titanium particles

At present, titanium implants inevitably release titanium particles into the surrounding tissues during implantation and long-term maintenance. To mitigate or slow the release of titanium particles, the first consideration is to surface-treat the implant to delay the corrosion rate and increase the resistance to friction.

A prevalent approach is to coat the implant surface, which considerably suppresses the release of titanium particles. Wang et al. [107] concluded that coating Nano-ZnO particles on implants promotes the corrosion resistance and antibacterial properties of implants. This surface modification strategy not only directly increase the corrosion resistance of implants, reducing the release of titanium particles, but it also indirectly affects the release of titanium particles as mentioned above. Wang et al. [108] found that applying calcined and uncalcined silicalite-1 coatings on titanium implants could bolster their corrosion resistance under inflammatory environment. In addition, alkali heat treatment and electrospinning can deposit nanowires on the titanium implant, forming nanoscale mesh structures that shield the underlying titanium from chemical corrosion.[109] Refining the grain size to the nanometer level can enhance the mechanical and chemical stability of titanium implants by reducing the internal strain and establishing the titanium dioxide layer. Electrochemical anodizing (EA) is another method that can be employed to boost the corrosion resistance and bioactivity of titanium-based implants.[110]

Studies have also been conducted on the conversion of pure titanium implants into titanium alloy implants. Akimoto et al. [111] found that titanium-zirconium alloy implants, especially when the molar ratio of zirconium is less than 50%, exhibit good corrosion resistance which can reduce the release of titanium particles. Wu et al. [112] analyzed the implant created by blending copper and titanium using various hybrid methods. They assessed the implants' potential antibacterial and corrosion -resistant capabilities and concluded that they have promising application prospects.

A more innovative strategy involves exploring new implant materials instead of relying on existing titanium-based implants. Wang et al. [113] concluded that tantalum and its derivatives show considerable application potential in orthopedic and dental implants due to their corrosion resistance, biocompatibility, bone integration ability and antibacterial properties. However, they noted that more research is required before these materials can be used in clinical application. Zirconium based implants have corrosion resistance and biocompatibility due to the formation of natural zirconia ($ZrO_2$) film. Many studies have modified the surface of zirconium based implants using various physical, chemical and biological methods to make them more suitable for clinical application, which is a promising development direction.[114] Implant materials made from cobalt-chromium-molybdenum alloy exhibit good mechanical properties and corrosion resistance, suggesting potential for future development in dentistry.[115] Polyether ether ketone (PEEK) is a synthetic polymer material that has been used as a biomaterial in orthopedics for many years.[116] Its similar mechanical and physical properties have given PEEK a wide range of application possibilities in oral implantology.[117] However, PEEK implants can lead to poor fiber encapsulation and bone integration, improving the biological activity of polyether ether ketone dental implants without compromising their mechanical properties presents a major challenge and a promising research direction.[117,118] Although exploring new materials can potentially avoid the release of titanium particles, it is crucial to ensure that these new material also meet other requirements for long-term maintenance of the implant. This makes the research more complex.

In conclusion, according to current understanding, inhibition of the release of titanium particles can be achieved by improving the metal alloy, or coating and modification of the coating to enhance the corrosion resistance and antibacterial properties of the implant. Although there is extensive research in this area, few have been successfully implemented in clinical practice, necessitating further exploration.

### Inhibit the pathogenic effect of titanium particles

Another direction to inhibit the development of titanium particle-induced peri-implantitis is to consider the pathogenic effect of titanium particles. Given that the specific role of titanium particles has not been fully clarified, the current treatment strategies primarily focus on the prevention and treatment of inflammation and osteolysis symptoms associated with peri-implantitis.

Eger et al. [119] demonstrated through experiments that either intraperitoneal injection or local implantation of slow-release membranes in the system around titanium implants, or local suppression of inflammation-related IL-1β, IL-6 and/or TNF-α expression could effectively inhibit the development of inflammation induced by titanium particles. Guo et al. [120] showed that a peptide segment adsorbed on titanium implants can increase the adhesion of osteoblasts and promote bone formation on the surface of titanium implants under inflammatory conditions. Jia et al. [121] also showed that applying an antibacterial coating to titanium implants could inhibit the absorption of bacteria and the formation of biofilm, and thus prevent inflammation. Similarly, Xiaoxiang et al. [122] showed that coating titanium implants with polydopamine nanoparticles, followed by a period of near-infrared light, can inhibit bacteria and reduce inflammation. Dextrorotatory-isoforms of amino acids (D-AAs) are vital components of the peptidoglycan in bacterial cell walls. They play a key role in bacterial adhesion to abiotic surfaces, promoting biofilm formation and its subsequent decomposition. This may be significant in preventing and treating peri-implantitis.[123] Gulati et al. [124] have summarized methods for implant surface modification to promote bone formation and soft tissue integration. They present strategies including topographical, chemical, electrochemical, biological, and therapeutic modifications. Interestingly, they propose that electrochemically anodized titanium implants can influence the nanomorphology of the implant surface, enhance biological activity, and facilitate local therapeutic release. This could be an effective strategy for managing inflammation. In addition, considering the potential pathogenic signaling pathway of titanium particles, as summarized above, substances like melatonin,[86,93] crocin,[94] etc., may be used as potential therapeutic drugs, and more studies are needed to confirm this.

However, the existing strategy primarily involve incorporating antibacterial and anti-inflammatory substances into the implant to inhibit the development of peri-implantitis. Since these substances are mostly synthesized by the respective research groups, there is a lack of follow-up promotion and clinical application examples. Furthermore, the connection between this effect and titanium particles remains clear. The strategy of inhibiting the development of peri-implantitis by inhibiting the pathogenic effect of titanium particles presents a wide area for future research.

## CONCLUSION AND FUTURE PERSPECTIVES

Peri-implantitis is a prevalent biological complication that presents the most challenging treatment in oral implantology. The traditional symptomatic treatment method often fail to accurately address the cause, resulting in unsatisfactory outcomes. Therefore, it is crucial to identify the progression of peri-implantitis and discover ways to alleviate and obstruct the development of inflammation to optimize the prevention and treatment strategies. Throughout the whole implant treatment process, titanium implants continuously release titanium particles to surrounding tissues due to drill wear, friction between implant and bone surface, wear caused by biomechanical load, biological friction corrosion effect and other factors. The role of titanium particles in the progression of peri-implantitis may be underestimated. In recent years, some studies have shown that the concentration of titanium particles in the tissue at the peri-implantitis site is significantly increased. However, these studies lack continuity. Most only describe the phenomenon of increased titanium particle content, without further exploring the possible mechanism. Moreover, due to the absence of a unified standard, there is limited value of comparison between different researches, thus limiting the evidence for the further exploration of the mechanisms. Future studies urgently need to establish a standardized process of sampling and examination to provide a basis for the rule of titanium particle release at the peri-implantitis site and subsequent mechanism research. Simultaneously, by comprehending the patterns of titanium particle release around implants, future research can use the release and distribution of titanium particles as a reference to find ways to inhibit their release. This could be an effective approach to mitigating the impact of titanium particles.

In recent years, there have been many studies on the proinflammatory effects of titanium particles. Some suggest that an excess of these particles induces a foreign body reaction. However, the presence of titanium particles was also detected around healthy implants, indicating that the foreign body reaction alone could not explain the increased concentration of titanium particles at the peri-implantitis site. It's worth noting that some epigenetic alterations may contribute to the pro-inflammatory effects of titanium particles, which vary depending upon the particle size. This requires a more precise detection method for the distribution of titanium particles around the implant, as described above. Drawing parallels with the adverse effects of wear particles after major joint replacement, titanium particles may regulate the development of inflammation and the process of osteolysis by affecting Wnt/β-catenin, NF-κB/RANKL/OPG and other signaling pathways. This offers promising directions for future research into the role of titanium particles in the peri-implantitis development. Studies also suggest a synergistic effect between titanium particles and bacteria in driving inflammation, hinting at a potential correlation between the influence of titanium particles and the risk factors for peri-implantitis. More longitudinal studies are needed to confirm this. In addition, Other areas of research such as autophagy, DNA damage, etc., further broaden our understanding of the role of titanium particles in the development of peri-implantitis. In future research, scholars should consider combining titanium particles with factors such as bacteria, autophagy, and DNA damage to explore potential synergistic effects. Signaling pathways related to inflammation development, such as Wnt/β-catenin and NF-κB/RANKL/OPG, require further attention to clarify the pathogenic mechanisms of titanium particles.

Because the role of titanium particles in the development of peri-implantitis remains to be clarified, means to inhibit their negative effects remain limited. Currently, the common method is to modify the surface of the implant. Techniques such as alkaline thermal method and electrostatic spinning technology are used to coat the implant, thereby inhibiting the release of titanium particles and potentially providing some anti-inflammatory effect. There is also ongoing research into innovative implant materials, including titanium alloys like titanium-zirconium and titanium-copper, which show potential for implant use. Other studies are considering tantalum, zirconium, peek biomaterials, etc. as alternatives to fundamentally mitigate the adverse effects of titanium particles. However, challenges abound in both implant modification and developing new implant materials. Factors such as biocompatibility of the implant, good bone bonding, adequate mechanical support, and the lack of other side effects of the new material all require further research. Moreover, titanium-based implants have proved to be commercially viable due to their excellent performance, even though the impact of titanium particles is not entirely established. This makes advancing research in this area particularly challenging. Another approach is to inhibit the pro-inflammatory effect of titanium particles by coating or loading the implant with anti-inflammatory and bacteriostatic drugs. However, this requires a deeper understanding of the role of titanium particles in the progression of peri-implantitis to achieve effective treatment. Therefore, a significant amount of work is still needed to better understand the role of titanium particles in both the area around the implant and the development of peri-implantitis. The mechanisms for both the inhibition of titanium particle release and the mitigation of their pathogenic effects remain largely unknown. These areas represent promising research directions that have yet to be fully explored. It is our hope that this review will provide new insights for further studies in this field.

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## AUTHOR CONTRIBUTIONS

M.S. conceived the of the presented idea. L.C., Z.T., H.L. and Y.Q. discussed the contents of this review. L.C., Z.T., H.L. and Y.Q. wrote the manuscript. X.G. and M.S. edited the manuscript. L.C. designed the table and figures.

## ADDITIONAL INFORMATION

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