

Systematic Review

Titanium Particle Impact on Immune Cells, Cytokines, and Inflammasomes: Helping to Profile Peri-Implantitis—A Systematic Review

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Abstract

Background: Peri-implantitis is an inflammatory condition caused by bacterial plaque and several factors like diabetes, smoking, titanium bio-tribocorrosion, implant–abutment micromovements, occlusal overload, cement remnants, and poor oral hygiene, resulting in bone resorption. The aim of this review was to evaluate the relationship between titanium metal particles and the development of peri-implantitis, specifically the characterisation of the inflammatory response regarding cytokine profile, immune cell infiltration, and transcription factors up-regulated in the peri-implant sites. **Methods:** A systematic review was conducted following the PRISMA guidelines, from January 2004 to January 2025, in three databases: PubMed, Web of Science, and Wiley Library. The inclusion criteria included in vivo human studies and in vitro studies with a focus on bio-tribocorrosion of titanium particles in peri-implant tissues, and their immunological and cellular implications. Quality assessment of in vivo transversal and case–control studies used Joanna Briggs Institute Critical Appraisal Tools, and, for in vitro studies, the modified CONSORT checklist. **Results:** A total of 27 studies were included, 20 in vitro and 7 in vivo. Titanium particles induced the secretion of IL-1 β , IL-6, and TNF- α by peri-implant cells, activation of the NLRP3 inflammasome, and RANKL/OPG bone resorption, further stimulating an exacerbated inflammatory response, LPS independent. There was a significant increase in IL-33, an alarmin, possibly associated with implant–pillar micromovements. IL-8 production by gingival stromal cells and fibroblasts, and downregulation of CCR7 can explain an altered leukocyte migration and the mixture of M1/M2 macrophage populations in peri-implantitis. **Conclusions:** Titanium particle bio-tribocorrosion stimulates a chronic inflammatory response impacting immune cell composition and cytokine secretion in peri-implant tissue, leading, ultimately, to osteolysis. Modulation of the immune response may contribute to the development of therapeutic strategies and the prevention of implant failure.

Keywords: corrosion; cytokines; dental implants; oral health; peri-implantitis; titanium ions; titanium particles



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1. Introduction

Case studies have estimated that approximately 5.8 to 16.9% of dental implants fail during the following 10–15 years [1]. The causes that negatively contribute to the longevity of dental implants have been investigated over the years by numerous authors. Regarding biological factors, two pathological entities have been widely described: peri-implant mucositis (PIM) and peri-implantitis (PI). These are inflammatory disorders associated with microbiological influences [2]. Both conditions initially involve the soft tissues around the osseointegrated dental implant and then culminate in a non-reversible process. The supporting crestal bone is then lost through the reabsorption process [3]. However, the distinction between the two inflammatory conditions is not yet entirely clear [4,5]. Regarding risk factors, several studies have been performed to assess and clarify the causes and risks of developing PI: previous history of periodontitis (PD), diabetes, smoking, poor oral hygiene, and inadequate plaque control [6]. Also, the pro-inflammatory microenvironment associated directly with the bacterial plaque can be affected by several other factors, like titanium bio-tribocorrosion, implant–abutment micromovements, occlusal overload, and cement remnants [7]. In recent years, attention has turned to the incidence of metal debris resulting from titanium wear found in peri-implant soft tissues. A relationship has been hypothesised between tribocorrosion, specifically metallic titanium particles, and the pathogenesis and progression of inflammatory disorders involving peri-implant tissues. It is noteworthy that *S. mutans*, primary colonisers of dental implant surfaces, are not present in PD, suggesting a specific bacterial habitat in the implant environment. On the other hand, *P. gingivalis*, which is associated with PI development, has greater adhesion when the implant surface already presents a high degree of corrosion. Particles released through corrosion act as a secondary inflammatory stimulus and are partially involved in the monocytic migration process and in osteoclastic proliferation and differentiation [8].

Furthermore, an upregulation of pro-inflammatory cytokines has been reported as a consequence of the debris released from dental implants, independently of the action of biological agents such as lipopolysaccharides (LPS).

Thus, titanium particles alone can trigger an inflammatory reaction [9]. Material degradation, including nano- and microparticles, activates the immune system by acting as foreign bodies with many inflammatory mediators and cytokines involved in the process. This is evidenced by titanium particles ranging in size from 0.25 to 7 µm. They induce the expression of IL-6, TNF-α, and IL-1β when in direct contact with macrophages. The secretion of IL-1β, results in an imbalance in the rate of bone remodelling and an increase in RANKL expression [10].

In addition, the titanium particles induce an increase in the synthesis of reactive oxygen species (ROS) in a time-dependent relationship. The particles are internalised through endocytosis, activating cells of the surrounding soft tissue like dendritic cells (DC), macrophages, fibroblasts, and epithelial cells, causing an abnormal migration of polymorphonuclear cells to the site, which exacerbates the local inflammatory response [11].

The aim of this review is to study the relationship between titanium metal particles and the development of PI. We defined the main outcomes as the characterisation of the inflammatory response regarding cytokine profile in the peri-implant sites, immune cell infiltration, and up-regulation of transcription factors.

2. Materials and Methods

This review observed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and was registered 14 November 2024 in the PROSPERO International prospective register of systematic reviews, under the number CRD42024608114.

An electronic search was performed in PubMed, Web of Science, and Wiley Online Library between the years 2004 and 2025 (PRISMA Checklist—Supplementary Material).

2.1. Review Question

The review focused on the search for current evidence regarding the contribution of bio-tribocorrosion to inflammation in dental implants, with emphasis on the wear of titanium particles and ions. More specifically, the main objective of this review was to clarify if titanium metal particles can influence the progression and pathogenesis of peri-implant inflammatory disorders. In this regard, the main outcome concerned the quantification of inflammatory cells present in situ (macrophages, polymorphonuclear cells, and lymphocytes); the analysis and characterisation of inflammatory cytokines; and the up-regulation of inflammatory transcription factors. An additional outcome was the detection of titanium particles in tissues and/or cells from failed dental implants. Thus, the PECO strategy was applied (Table 1).

Table 1. PECO strategy for formulating the research question.

P (Population)	Human observational studies and experimental assays (in vitro)
E (Exposure)	Effect of titanium particles resulting from bio-tribocorrosion in peri-implantitis inflammatory reaction
C (Comparison)	Healthy titanium dental implants
O (Outcomes)	Inflammatory response and cytokine production; cell activation and viability

2.2. Screening Process

The search strategy for the PubMed database was as follows: MeSH terms—dental implants “[Title/Abstract]”, peri-implantitis “[Title/Abstract]”, corrosion “[Title/Abstract]”, and relevant keywords—titanium particles “[Title/Abstract]”, titanium ions “[Title/Abstract]”, to ensure comprehensive coverage of the literature. Boolean operators (“AND” and “OR”) were used to relate the above terms to each other. The appropriated keywords were adapted to the specific syntax and indexing of each of the other two databases. For each database, two independent searches were conducted with the listed combinations, to maximise retrieval of results, which were exported to the Zotero v7.0.13 platform for reference management.

2.3. Eligibility Criteria

The articles that have been included concern the effect of bio-tribocorrosion of titanium particles around peri-implant soft tissues and their immunological and cellular implications. Animal studies were excluded because bio-tribocorrosion is not only associated with factors like food, infection, oral hygiene products, age, and others, making animal models inappropriate to compare results. Also, studies involving implantoplasty and implant scaling were excluded, as the focus of the review was not implant surface and PI treatment but titanium particles, tribocorrosion, and the immune microenvironment in the peri-implant tissue.

All grey literature was excluded—review papers, correspondence, personal viewpoints, book sections, conference proceedings, and abstracts—and a manual search was conducted, reviewing the reference lists of the included studies and relevant systematic reviews.

Full-text and open-access articles were considered for the research, between January 2024 and January 2025; only findings and reports in English were analysed for the preparation of this document, and the criteria used for the screening process are described in Table 2.

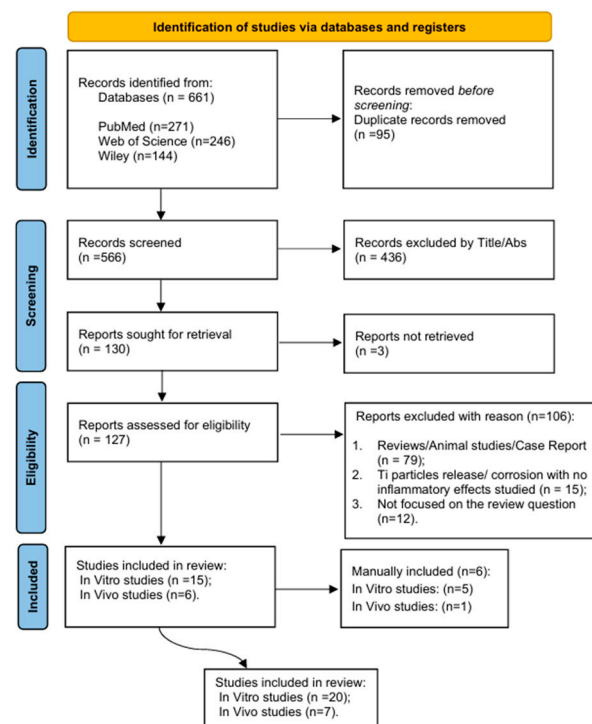
Table 2. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
In vivo studies in humans, such as cohort studies, cross-sectional investigations, case-control analyses, and randomised trials	In vivo animal studies
In vitro studies	Studies concerning the wear of titanium particles in organs other than the oral cavity
	Studies in which titanium particles resulted from debridement treatments (implantoplasty and implant scaling)
	Studies with a focus on evaluating the effects of implant-abutment connection compatibility and cover screw design on peri-implant disease
	Review papers, correspondence, personal viewpoints, book sections, conference proceedings, and summaries

2.4. Data Extraction

Data were extracted independently by two reviewers (MF and SS) into evidence tables. Inter-reviewer confidentiality was strictly ensured during the preparation of the manuscript, as each reviewer was independently assigned to a specific methodological domain to avoid any potential influence or bias. A total of 27 articles were selected for integral reading, of which 20 were in vitro studies and 7 were in vivo. Two independent evaluators (MF and SS) collected data, which was then compiled into evidence tables: Author, Year; Ti Particles/Size; Cell Line/Model; Inflammatory Biomarker; Assay; Summary.

The article selection process is specified in the PRISMA flow diagram—Figure 1.

**Figure 1.** Fluoxogram PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

2.5. Quality Assessment

The quality assessment (QA) on the included publications was carried out by two independent reviewers (MF and SS), and any disagreement was resolved through discussion

with a third reviewer (JM). Each bias risk analysis was conducted blindly among the reviewers, and only at the end of the assessment process was the final decision made unanimously.

To assess the risk of bias of the in vivo studies, both cross-sectional and case-control, JBI (Joanna Briggs Institute Critical Appraisal Tools) tools were used. Reports were thus divided based on typology, and each study was analysed considering the appropriate checklist. Eight questions were included for cross-sectional studies and ten questions for case-control studies. For both checklists, the risk of bias was classified as “<50%=high risk”, “50 up to 69%=moderate risk”, and “>70%=low risk” when the study achieved a “yes” percentage score in each. The results of the verified studies are shown in Table S1A,B—Supplementary Material.

To assess the risk of bias of the in vitro studies, the Modified CONSORT checklist was implemented since it has been identified as a useful tool for issues related to dentistry, as proposed by Faggion “*Guidelines for Reporting Pre-clinical In Vitro Studies on Dental Materials*” [12]. This checklist contains 14 items enabling the assessment of each study concerning standard criteria: background, objectives, intervention, outcomes, and sample size. Subsequently, concerning randomization, the checklist included the following methods: sequence generation, allocation concealment mechanism, implementation, blinding, and statistical methods. Finally, outcomes, limitations, funding, and protocol were also included in the checklist. Each item correctly reported was marked YES. The YES score of 14 indicates higher quality. The results of the QA are shown in Table S2—Supplementary Material.

Considering in vivo studies and the JBI quality criteria, five studies had no risk of bias (3 cross-sectional and 2 case-control), and two had a moderate risk of bias (cross-sectional) (Figure 2).

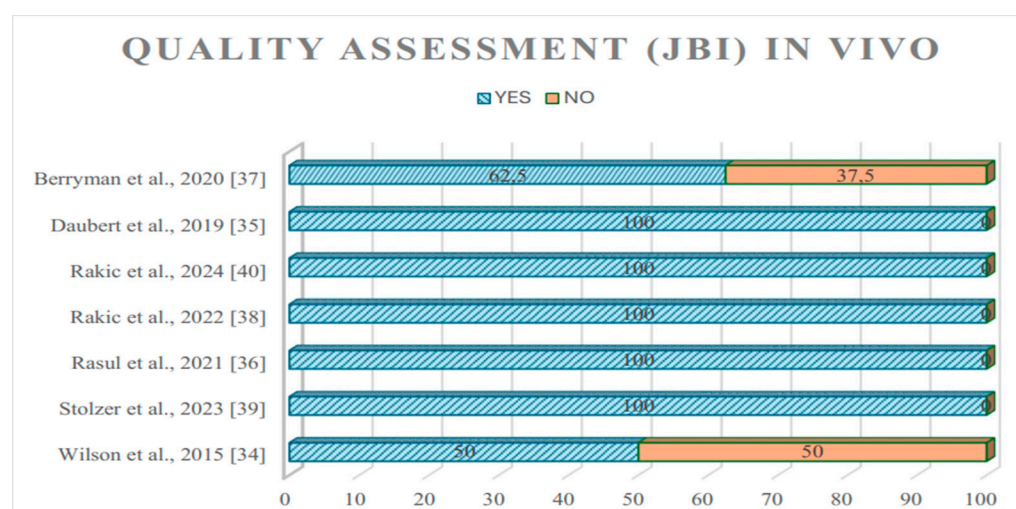


Figure 2. Summary chart of JBI QA results for in vivo studies.

For in vitro studies, the modified CONSORT checklist was used from “*Guidelines for Reporting Pre-clinical In Vitro Studies on Dental Materials*” proposed by Faggion [12].

Considering the key methodology reported in the twenty in vitro studies on dental materials, the median quality assessment score was 8 out of 14. The lowest score was 7, and the highest score was 9. It should also be emphasised that only half of the articles provide information regarding external funding. As stated by previous authors [13], all experimental investigations had similar failing domains: “sample size determination, random sequence generation, allocation concealment, implementation details, blinding, and publication of the full study protocol.” (Figure 3).

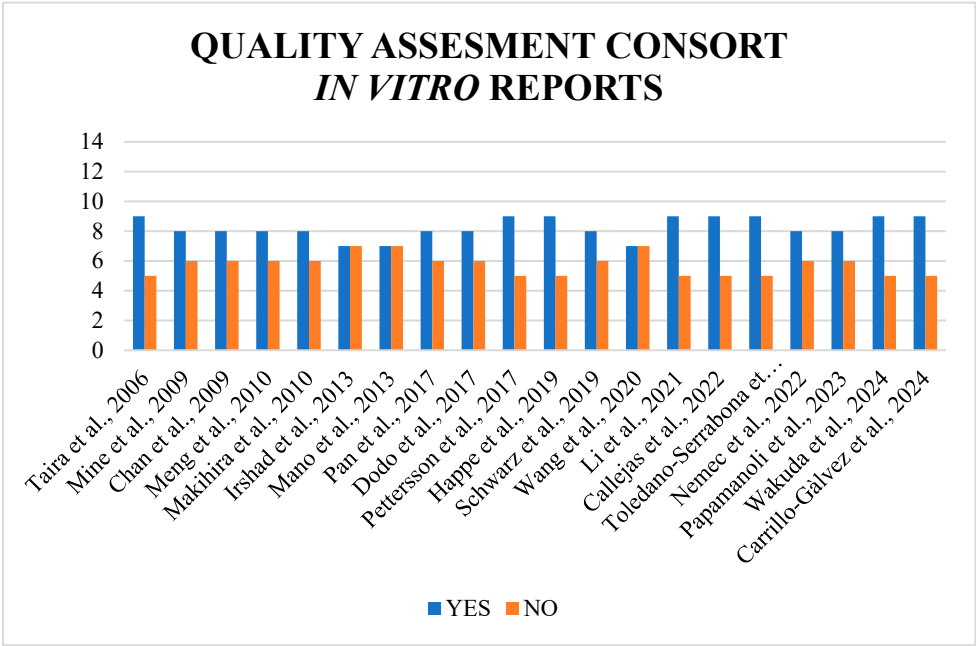


Figure 3. Summary chart of modified CONSORT QA results for in vitro studies.

To obtain an overall view of the results, we decided to transfer the information from the reports into a table (Table 3), considering parameters previously defined as important for the proposed review. Considering the size of the particles encountered, the cell lines used, and the type of tissue sampled, the inflammatory target of the study, the type of assay performed on the various samples, and, finally, including a summary of the main results.

Table 3. Characteristics of included studies.

In Vitro Studies					
Author, Year	Ti Particles/Size	Cell Line/Model	Inflammatory Biomarker	Assay	Summary
Taira et al., 2006 [14]	Ti ions 1 ppm	Macroph.RAW264 (mice)	TNF-α	ELISA	Cultures with Ti show increased SOD and TNF-α secretion: uptake of Ti-containing complex by macrophages induced oxidative stress and triggered inflammatory response.
Chan et al., 2009 [15]	Ti ions (0–100 μm)	Dendritic cells, blood derived (human)	MHCII, CD80, CD86, CD40, CD54, CD25, CCR4, CCR6 and CCR 7, IL-1β, IL-6, IL-12, TNF-α, IL-4, IL-10, TGF-β1, TGF-β2, TGF-β3, CCL17, CCL22	Flow cytometry, ELISA	Uptake of Ti ions by DCs (membranes, cytoplasm, and nucleus). DCs decreased expression of MHCII, CD80, CD86, CD40, CD54, CD25, CCR6, and CCR7, showing a weaker immunological synapse with T lymphocytes (only CCR4 slightly increased); Th1 cytokine IL-12 improved substantially as lymphocyte stimulatory capacity increased. Titanium modifies DC functions, leading to increased T lymphocyte activation and a shift towards a Th1-type immune response.
Makihira et al., 2010 [16]	Ti ions (1–19 ppm)	Gingival epithelial (mice)	CCL-2, TLR-4, ICAM-1	RT-PCR	Ti ions increased CCL2 regulation in GE subjected to LPS originating from <i>P. gingivalis</i> synergistically; they also increased TLR-4 and ICAM-1 expression. This suggests that Ti ions partially contribute to monocyte infiltration in the oral cavity by increasing the responsiveness of gingival epithelial cells to microbial stimuli.
Meng et al., 2010 [17]	Ti part 1 μm	Osteoclasts (mice)	TRAP, CAT K, CAII	RT-PCR	Ti particles were phagocytosed; osteoclast activity was enhanced (TRAP and CAT K) at a lower concentration of Ti particles but inhibited at high.
Mine et al., 2010 [18]	Ti ions (1–9 ppm)	Gingival epithelial cells (GE), osteoclasts RAW264.7, and osteoblasts MC3T3-E1 (all mice)	TRAP, CAT K, RANKL, OPG, Runx2, Osterix, COL-1	RT-PCR	Ti ions at 9 ppm suppressed the expression of Runx2, Osterix, and COL-1 in osteoblast-like cells and increased RANKL and OPG expression. In osteoclasts and in GE, no effect on TRAP and CAT K (reported previously for this cell line development with RANKL). Ti ions impair osteoblast differentiation and modify the RANKL/OPG gene expression ratio, which is associated with osteoclast differentiation.

Table 3. Cont.

Author, Year	Ti Particles/Size	Cell Line/Model	In Vitro Studies		Summary
			Inflammatory Biomarker	Assay	
Irshad et al., 2013 [19]	Ti par (<5 µm)	Fibroblasts (human) biopsy	TNF-α, IL-6, IL-1β, IL-8, MCP-1	RT-PCR, ELISA	Ti particles and <i>P. gingivalis</i> , independently, are capable of eliciting pro-inflammatory responses in PIGFs: TNF-α, IL-6, and IL-8 (alone) or TNF-α and MCP-1 (combined); IL-1β induced only by <i>P. gingivalis</i> .
Mano, 2013 [20]	Ti par (25 nm)	Pulmonary epithelial (NCI-H292) human	LPS binding protein, CD14, TLR-4, IL-6	RT-PCR, Flow-cytometry	TLR 4, but not LBP or CD 14, plays a role in the internalisation of Ti particles to cells and in the inflammatory signal transduction mediated by Ti particles. The latter association was seen by the increased IL-6 expression.
Dodo et al., 2017 [21]	Ti par (<20 µm and 21 nm)	Macro. THP-1 (human)	TNF-α, IL-1β, IL-6	RT-PCR, ELISA	Ti nano or microparticles and LPS (<i>P. gingivalis</i>) and macrophages impacted viability and inflammation—gene expression and cytokine release were significantly greater for TNF-α and IL-1β after 12 h, and for IL-6 but only 24 h later. There is robust pro-inflammatory response in nanoparticles independent of LPS presence.
Pan et al., 2017 [22]	Ti ions	Fibroblasts L929 (mice)	CASP-9, CASP-3	RT-PCR	Ti particles have a cytotoxic effect on fibroblasts (time-dependent): upregulation of CASP-9 and CASP-3 and apoptosis by the intrinsic pathway. Apoptosis might not be a result of the ions released but of compromised cell adhesion and subsequent cell apoptosis.
Pettersson et al., 2017 [23]	Ti ions	Macro. THP-1 (human)	NLRP3, ASC, CASP-1, IL-1β, IL-1a, b, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, IFN-γ, TNF-α, GM-CSF	RT-PCR, ELISA	Ti ions stimulated inflammasome activation: IL-1β release. LPS exposure enhances this effect. Nevertheless, Ti ions alone did not promote transcription of the inflammasome components. Ti ions establish particles that represent a secondary stimulus for a pro-inflammatory response.
Happe et al., 2019 [24]	Ti part < 20 µm	Gingival fibroblasts and osteoblasts (human)	TNF-α, IL-6	ELISA	Ti particle concentration affects cell growth and proliferation and has cytotoxic effects, especially in GF; osteoblasts produce IL-6 only 24 h after contact, but GF produce IL-6 continuously for 21 days. Ti particles were identified inside the cells.
Schwarz et al., 2019 [25]	Ti part (60–100 nm)	Gingival fibroblasts and osteoblasts (human), macrophage THP-1 (human)	IL-1β, IL-6	ELISA	Increasing Ti particle concentration correlates negatively with cell viability both in osteoblasts and GF. No significant improvement in IL-1β and IL-6 concentrations was observed in THP-1. Thus, no pro-inflammatory effects.
Toledano-Serrabona et al., 2020 [26]	Ti part. (30–70 nm)	Macrophage THP-1 (human) and bone marrow-derived mesenchymal stem cells-BM-MSCs (human)	CCR7, TNF-α, IL-1β, CD206, TGF-β, IL-10	RT-PCR, ELISA	Macrophages stimulated by Ti particles developed an amplified pro-inflammatory expression of TNF-α and a reduced expression of TGF-β and CD206. Regarding cytokine release, there was an increase in IL-1β, whereas IL-10 was reduced. Ti particle concentration negatively correlates with BM-MSCs cell viability, and the cells showed a significant decrease in Runx2 and OC expression—osteogenic response markers. Ti particles elicit a pro-inflammatory response and suppress osteogenic gene expression.
Wang et al., 2020 [27]	Ti ions 10–50 µm	Osteoblasts (human)	mROS, SOD, SIRT	Western blot	Ti ions reduced osteoblast capability. With improved Ti ion concentration, the expression levels of LC3 gradually increased, P62 reduced, autophagic flow amplified, and mROS levels improved. In addition, activity of SOD2/SIRT 3 decreased.
Callejas et al., 2022 [28]	Ti part (5–30 µm)	Macrophage THP-1 (human)	TNFα, IL-1β, CCR7, IL-10, TGF-β, CD206, TNFα, IL-1β, IL-10	RT-PCR, ELISA	Smaller Ti particle sizes show less cytotoxicity. At non cytotoxic concentrations, TNFα and IL-1β expression, inflammatory indicators, were higher related to bigger Ti particles: particles of 15 µm showed a minor pro-inflammatory and higher anti-inflammatory reaction as categorised by gene expression and cytokine release: biocompatible and reveal a lower immune response.
Li et al., 2022 [29]	Ti part (<5 µm and <100 nm)	Gingival fibroblasts (human)	FAK, fibronectin, COL-1	RT-PCR, Western blot	Ti nanoparticles significantly inhibited GF cell viability, proliferation, and migration compared with microparticles. Additionally, they caused cytoskeleton disruption as measured by protein expression. This effect was enhanced with LPS.
Nemec, 2022 [30]	Ti part (<100 nm) nano	Gingival mesenchymal stromal cells (human)	IL-6, IL-8, MCP-1	RT-PCR, ELISA	Cell proliferation and viability were inhibited by Ti nanoparticles (<100 nm). They also elicited strong expression of IL-8, and this response was enhanced by LPS.

Table 3. *Cont.*

In Vitro Studies					
Author, Year	Ti Particles/Size	Cell Line/Model	Inflammatory Biomarker	Assay	Summary
Papamanoli, 2023 [31]	Ti part (10.4 ± 6.4 µm)	Gingival fibroblasts (human)	IL-6, IL-8, Col-1a	RT-PCR	Association of Ti particles and LPS substantially increased expression of IL-6, IL-8, and Col-1a. It seems that particles may stimulate comparable reactions to the endotoxin, whereas synergistically amplifying it.
Carrillo-Galvèz et al., 2024 [32]	Ti ions	Bone derived mesenchymal stromal cells (human)	NLRP3, AIM2, IL-1 β	RT-PCR, ELISA	There is induction of NLRP3 and absence of AIM2 inflammasome pathways facilitated by bacterial factors, with increased release of IL-1 β. Bacterial agents, in combination with Ti ions, enhance NLRP3 expression while AIM2 is reduced. The progression of inflammation in peri-implantitis may be more critical due to the mutual effect of organic and inorganic elements that enhance NLRP3 inflammasome activation.
Wakuda et al., 2025 [33]	Ti par 25 µm (30–100 µg/mL)	Gingival epithelial (Ca9–22) (human)	COX2, ROS, TGF-β 1, NLRP1, NLRP3, CASP1, IL-1 β	RT-PCR, ELISA	Cells treated with Ti particles showed an increase of 75% in cell capability through all dilutions. Inflammation-related genes (COX2 and TGF-β1) substantially intensified in a dose-dependent way. NLRP3 and CASP-1 expression increased, as well as the secretion of IL-1 β. Moreover, there were improved ROS levels after testing with Ti particles.
In Vivo Human Studies					
Author, Year	Ti Particles/size	Cell Line/model	Inflammatory Biomarker	Assay	Summary
Wilson et al., 2015 [34]	Ti particles	36 peri-implantitis (biopsies)	Chronic inflammatory infiltrates—plasma cells; MGNCs	Histological analysis	Chronic inflammatory infiltrates—plasma cells; Multinucleated Giant Cells (MGNCs) were observed.
Daubert et al., 2019 [35]	Ti particles	21 peri-implantitis, 24 healthy implants (PICF and biopsies)	DNA methylation	ELISA	Increased levels of methylated DNA in peri-implantitis; association of Ti levels and global methylation, independent of peri-implantitis, suggesting methylation may be affected by Ti dissolution products.
Rasul et al., 2021 [36]	Ti particles	30 peri-implantitis, 20 healthy implants (biopsies)	Peri-implantitis parameters (probing depth, plaque index, gingival index)	Mass spectrometry	Notably higher Ti level in submucosal plaque surrounding dental implants with symptoms of peri-implantitis compared with healthy dental implants.
Berryman et al., 2020 [37]	Ti particles	10 peri-implantitis (biopsies)	TGF-β 1, RANKL, IL-33, and CD68	IHC, ELISA	Tissue samples showed a mixed chronic inflammatory infiltration. Substantial upregulation of cytokine RANKL detected, with a tendency toward overexpression of IL-33 and TGF-β1 in areas with Ti.
Rakic et al., 2022 [38]	Ti particles	39 peri-implantitis, 35 periodontitis (biopsies)	CD68, IL-6, NF-k β, and VEGF	IHC and histological analysis	Neutrophil infiltration inside the granulation matrix, absence of MGNCs or specific inflammatory patterns, severe neovascularization, and persistent immune cell infiltration mainly composed of plasma cells, neutrophils, and macrophages—high CD68 and VEGF.
Stolzer et al., 2023 [39]	Ti particles	20 peri-implantitis, 20 healthy implants, 20 no implants (peripheral blood)	TNF-α, IL-1 β	ELISA	Significant relationship of positive Ti stimulation and clinical and radiological peri-implantitis; macrophages in 28.3% of individuals across all groups emitted pro-inflammatory cytokines beyond normal biological levels.
Rakic et al., 2024 [40]	Ti particles	36 peri-implantitis, 36 peri-implant mucositis, 39 healthy implants, and 37 periodontitis (PICF and biopsies)	Chronic inflammatory infiltrates, MGNCs, and VEGF	IHC and histological analysis, ELISA	TPs were detected as unbound material enclosed within granulation tissue, but no MGNCs or impaired phagocytes were observed—no evidence of foreign body response or distinct pathological impact caused by TPs in peri-implantitis. VEGF is markedly upregulated in peri-implantitis relative to periodontitis and shows a positive association with its soluble levels in PICF.

Notes: ELISA, enzyme-linked immunosorbent assay; SOD, Superoxide dismutase; DC, dendritic cell; RT PCR, reverse transcription polymerase chain reaction; GE, gingival epithelial; LPS, lipopolysaccharide; CCL2, chemokine (C-C motif) ligand 2; TLR-4, toll-like receptor 4; ICAM-1, intercellular adhesion molecule 1; TRAP, tartrate-resistant acid phosphatase; Cat K, cathepsin K; CAII, carbonic anhydrase II; RANKL, receptor activator of nuclear factor kappa beta; OPG, osteoprotegerin; Runx2, runt-related transcription factor 2; COL-1, type I collagen; PIGFs, peri-implant gingival fibroblasts; MCP-1, monocyte chemoattractant protein-1; LBP, ligand-binding domain; GF, gingival fibroblasts; OC, Osteoclasts; mROS, mitochondrial reactive oxygen species; LC3, microtubule-associated proteins 1A/1B light chain 3B; IHC, immunohistochemistry; TPs, titanium particles; PICF, PICF, peri-implant crevicular fluid.

3. Results

After analysing the 27 articles, it was decided to summarise the results, categorising them according to critical parameter size of titanium particles and cell type, for a better overall understanding. The results were then grouped into three areas of interest, considering quantification and evaluation in terms of secretion/expression of interleukins and TNF- α , transcriptional factors, inflammasomes, and other mediators of inflammation, and finally expression of chemotactic and growth factors (Tables 4–6).

Table 4. Interleukin and tumour necrosis factor.

In Vitro Studies									
Author, Year	Ti Particles/Ions Size	Cell Type	TNF- α	IL-6	IL1- β	IL-8	IL-12	IL-10	IL-33
Taira, 2006 [14]	Ions	Mac	↑						
Chan, 2009 [15]	Ions	DC					↑	↓	
Irshad, 2013 [19]	part.: <5 μ m	Fib	↑	↑		↑			
Mano, 2013 [20]	part.: <25 μ m	Epi		↑					
Dodo, 2017 [21]	part.: <21 nm	Mac	↑	↑	↑				
Pettersson, 2017 [23]	Ions	Mac			↑			↑	
Happe, 2019 [24]	part.: <20 μ m	Fib		↑					
Toledano-Serrabona, 2022 [26]	part.: (30–70 nm)	Mac	↑		↑			↓	
Callejas, 2022 [28]	part.: 5–30 μ m	Mac	↑		↑			↑*	
Nemec, 2022 [30]	part.: (100 nm)	GSC				↑			
Papamanoli, 2023 [31]	part.: (15 μ m)	Fib		↑		↑			
Wakuda, 2025 [33]	part (25 μ m)	Epit			↑				
TOTAL			5	5	5	3	1	4	0
In Vivo Studies									
Author, Year	Ti particles/Ions Size	Cell/Tissues	TNF- α	IL-6	IL1- β	IL-8	IL-12	IL-10	IL-33
Berryman, 2020 [37]	-	PIT Biopsy							↑
Stolzer, 2023 [39]	-	PB Mon/Mac	↑		↑				
TOTAL			1		2				1

Notes: Mac, macrophages; DC, dendritic cells; Fib, fibroblasts; Epit, epithelial cell line; GSC, gingival stromal cells; PIT, peri-implant tissue; PB, peripheral blood; Mon, monocytes; Mac, macrophages; *: only with 30 μ m Ti particle.

Table 5. Transcriptional factors, Inflammasome and other inflammatory-related markers.

In Vitro Studies									
Author, Year	Ti Particle/Ions	Cell Type	TLR4	RANKL	OPG	CASP-1,9,3	NLRP3	AIM2	COX-2
Mine, 2009 [18]	ions	GinE Ostb/Ostc		↑	↑				
Makihira, 2010 [16]	ions	GE-1 Epit	↑						
Mano, 2013 [20]	par.: <25 nm	Epit	↑						
Pan, 2017 [22]	ions	Fib				↑			
Pettersson, 2017 [23]	ions	Mac				↑	↑		
Carrillo-Gálvez et al., 2024 [32]	ions	HMSC					↑		
Wakuda, 2025 [33]	par.: (25 μ m)	Epit				↑	↑		↑
TOTAL			2	1	1	3	3		1
In Vivo Studies									
Author, Year	Ti Particle/Ions	Tissues	TLR4	RANKL	OPG	CASP-1,9,3	NLRP3	AIM2	COX-2
Berryman, 2020 [37]	-	PIT biopsy		↑					
TOTAL				1					

Notes: GinE, gingival epithelial cells; Ostb, osteoblasts; Ostc, osteoclasts; Epit, epithelial cell line; Mac, macrophages; hMSC, human mesenchymal stem cells; Fib, fibroblast; PIT, peri-implant tissue; GE-1, gingival epithelial-like cells.

Table 6. Chemokines and growth factors.

In Vitro Studies						
Author, Year	Ti Particles/Ions Size	Cell Type	CCR7	MCP-1	TGF-B	VEGF
Chan, 2009 [15]	Ti ions	DC	↓		↓	
Irshad, 2013 [19]	par.: 5 µm	Fib		↑		
Toledano-Serrabona, 2022 [26]	par.: (30–70 nm)	Mac	↓		↓	
Callejas, 2022 [28]	Ti part (5–30 µm)	Mac	↓ *		↑	
Nemec, 2022 [30]	part.: (100 nm)	GSC		↓		
Wakuda, 2025 [33]	par.: (25 µm)	Epit			↑	
TOTAL			3	2	4	
In Vivo Studies						
Berryman, 2020 [37]	-	PIT Biopsy			↑	
Rakic, 2022 [38]	-	PIT Biopsy				↑
Rakic, 2024 [40]	-	PIT Biopsy PICF				↑ *
TOTAL					1	2

Notes: DC, dendritic cells; Fib, fibroblast; Mac, macrophages; GSC, gingival stromal cells; Epit, epithelial cell line; PIT, peri-implant tissue; PICF, peri-implant crevicular fluid; *: Only 30 µm particles.

4. Discussion

Bio-tribocorrosion is the surface wear/breakdown of dental implants caused by mechanical, chemical, and electrochemical interactions, under biological conditions, like the oral cavity environment. Titanium micro- and small nanoparticles, resulting from bio-tribocorrosion when in contact with cells, induce alterations in gene expression and cytokine production, changing the inflammatory response and stimulating bone resorption. In particular, particles ranging from 0.25 to 7 µm can be internalised via phagocytosis or pinocytosis by neutrophils, macrophages, and DCs. Larger titanium particles can also activate a cellular immune response without being internalised.

The studies included in this review, both in vivo and in vitro, confirm the association between the inflammatory response in peri-implantitis and the dissolution products of titanium dental implants, i.e., bio-tribocorrosion. This process is dependent on the type of particle observed, its size, and the time during which the particles or ions interact with the surrounding biological environment.

Considering the association between pro-inflammatory interleukins and exposure to different sizes of titanium particles, the included studies point to an increase in the expression levels of IL1-β, TNF-α, and IL-6 produced by macrophages, epithelial cells, and fibroblasts [14,19,21,24,26,28,31,33,39]. These findings agree with several studies indicating the same cytokine increase in PIT either by protein expression or immunohistochemical analysis. Ultimately, TNF-α induces RANKL expression, modulating the balance of RANKL/OPG and stimulating bone resorption, as observed by Mine and others, when coculturing titanium particles with osteoblasts [10,18,41,42].

IL-1β, is a pro-inflammatory cytokine, produced by several cells, like macrophages, neutrophils, and DCs, with a key role in immune regulation, especially in connective tissue and bone: it inhibits the formation of type I fibrillar collagen and induces osteoclast activation. TNF-α, another pro-inflammatory cytokine produced rapidly after infection, mainly by macrophages, has numerous effects like prostaglandin synthesis, cell proliferation and differentiation, and tumorigenesis initiation. It also induces osteoclast activation, affecting

the balance of RANKL/OPG. IL-6 is a pleiotropic cytokine, produced by immune cells, fibroblasts, endothelial cells, and others, associated with inflammation, immune response, and haematopoiesis. It is produced in response to infection and tissue damage such as trauma, with high levels being detected around failed implants. Previous authors showed, both in vivo and in vitro, IL-6, IL-1 β , and TNF- α up-regulation in PIT, stimulating the inflammatory response. The soft tissue destruction and bone resorption, induced by titanium particles are clinically translated into PI and implant failure.

Continuing to focus on the interleukins, an in vivo, cross-sectional study involving ten biopsies from patients with PI found significant upregulation of IL-33, which was more pronounced in tissue areas with higher titanium particle concentrations [37]. A recently discovered cytokine, IL-33, has been found to play a central role in several diseases, such as rheumatoid arthritis, asthma, Sjogren's syndrome, and also PD [43]. IL-33 is abundantly produced by endothelial, epithelial, and fibroblast stromal cells in human and mouse tissue. Unlike other cytokines, it is already present in normal tissue, rising very quickly after endothelial cell damage or mechanical injury; hence, it is referred to as an alarmin [44]. From our results, it can be suggested that parallel with the production of IL-1 β , IL-6, and TNF- α triggered by titanium particle phagocytosis, IL-33 is released as a result either from the initial drilling procedure at implant placement or later as a result of biomechanical stress induced by micromovements at the implant–abutment interface. These, associated with functional loading during masticatory activity and the presence of microgaps, together can provoke repetitive mechanical stimulation of PIT.

In this review, another trend was also observed, mainly the production of IL-8 by both gingival stromal cells and fibroblasts, in contrast to earlier studies, that mark this chemokine as unaltered in PI [45]. IL-8 is important in the recruitment of neutrophils and macrophages during inflammation. In fact, by testing the effects of exposure to particles derived from the degradation of titanium, in vitro studies showed an increase in IL-8 production, independent of the biological influence of LPS [19,30,31]. Studies on total hip replacement point out that M1 macrophages can induce IL-8 production and affect the inflammatory response in response to titanium wear particles, causing osteoblast/osteoclast imbalance [46]. Our results reinforce a role for IL-8 in PI that, together with other cytokines like IL-1 β , can change the adaptive immune response and lead to implant failure. Very recently, new data from transcriptome analysis of peri-implant gingival tissues have shown an upregulation of IL-8 expression [47].

Similarly, two in vivo studies have shown that VEGF expression was markedly higher in PI than in periodontitis, both in biopsies and PICF. Nevertheless, despite titanium particle detection in granulation tissue from the biopsies, a direct effect cannot be inferred [38,40]. VEGF, an angiogenic and vasculogenic factor, produced by immune cells, is associated with persistent inflammation and progression of gingivitis to periodontitis [48]. Despite its role in PI not being very clear, it can act independently or in combination with TNF- α , enhancing osteointegration and wound healing. In titanium particle-induced peri-prosthetic osteolysis, VEGF was proposed as a biomarker. In PI, despite VEGF presence in samples from PICF of patients, further studies are necessary as there is no histopathological pattern associating titanium particle presence and VEGF.

Regarding the inflammasome NLRP3, an innate protein receptor, downstream of TLR-4, a regulator of CASP-1 and immune response to infectious agents, an up-regulation was observed. This response to titanium particles was detected in macrophages, epithelial cells, and mesenchymal stromal cells. This cellular response was paralleled by IL-1 β production and enhanced by LPS [23,32,33]. These are the first in vitro reports of NLRP3 activation by titanium particles, specifically in PI. One study in human PI biopsies observed increased expression of NLRP3/AIM2 inflammasomes, CASP-1, and IL-1 β , and, in mice, NLRP3

inflammasome upregulation induced periapical lesions. Thus, neither accessed the cellular response to the presence/absence of titanium wear debris [49,50]. It is clearer that both bacterial and titanium/metal particles can activate innate immune cells in PI and cause IL-1 β -osteolysis. As a result, NLRP3 could be an efficient diagnostic biomarker.

Furthermore, considering chemotactic factors, for the first time, a decrease in CCR7 is emphasised. Firstly, a study conducted on DCs showed, following exposure to titanium ions, a significant reduction in the expression of CCR7 as well as various molecules such as CD40, CD54, CD80, and CD86 [15]. A decrease in CCR7 expression can impair normal DC movement, leading to chronic inflammation. In addition, in macrophages a significant decrease was observed in CCR7 expression, tested either alone or with LPS [26,28]. In macrophages, this result can reflect a reduced migration capacity but also a shift in macrophage phenotype from M1 to M2. In the first study, this is backed by the common decrease in CCR7 and the anti-inflammatory markers TGF- β and IL-10. In the second study by Callejas and colleagues, the decrease was also observed, except with the larger titanium particles. Thus, in PI there is a mixed M1 and M2 population that can be helpful when testing PI treatments, directing the immune response towards M2 polarisation [51]. In addition, the use of carriers for the direct target of peri-implant tissue is already under evaluation. Techniques that increase the thickness of the peri-implant soft tissue include the use of titanium prepared platelet-rich fibrin (T-PRF), also used in other dental treatments [52].

Regarding the cytotoxic effect of titanium debris, in this review, for the first time, a study quantifying DNA methylation both in PICF and biopsies, showed that the group with PI had higher levels of methylation (5 mC) compared to the control group. This result was further enhanced in tissues adjacent to titanium particles. Thus, epigenetic fluctuations and global DNA methylation are closely linked to the presence of titanium particles in PI [35]. However, recent works on PI “molecular signatures” and epigenomes were more cautious about associating epigenetic changes in oral cells treated with titanium particles [53]. This latest finding leads us to hypothesise that epigenetic variations can be explained not only by the cellular interaction with titanium particles but also by a wider interaction with organic compounds in the environmental medium.

Histology of the PI biopsies showed a mix of chronic inflammatory infiltration of neutrophils, macrophages, and plasma cells consistent with chronic inflammation. Regarding foreign body reaction (FBR), recent studies did not detect the presence of MGNCs in biopsies from PI patients [38,40]. In the other in vivo human study, Wilson and colleagues observed this presence in 34 of the 36 biopsies of PI, although only 7 revealed the presence of titanium particles [34]. Furthermore, titanium particles are known to be present in the oral cavity because of food or toothpaste ingestion regardless of dental implants. MGNCs result from macrophage fusion and are commonly seen in response to biomaterials. Their presence can indicate titanium particle phagocytosis depending on the size: less than 25 μ m. Furthermore, they can be associated with wound healing after chronic inflammation [54,55]. Taken together with our results regarding CCR7 decrease and IL-8 production, macrophages, either M1 or M2, are part of the cell populations in the peri implant tissue. They are a key factor in the inflammatory process, but if we do not see MGNCs, we can infer that the immune response is shifting towards an anti-inflammatory state and the implant survives. Also, neutrophils initial recruitment may condition the following immune response. Thus, this suggests that FBR may not be a result of titanium wear and a secondary cause of implant failure, not providing sufficient evidence to be considered a risk factor.

4.1. Future Perspectives

The studies included in this review confirm the direct effect of titanium particles on implant bone resorption. The findings of titanium particles in proximity to dental implants and sites with PI, together with the exacerbated production of TNF- α , IL-6, and IL-1 β , clearly affect the osteoblast/osteoclast balance. At the present time, most of the clinical interventions aim to reduce the particles released into the peri-implant tissue by avoiding friction between the implant and alveolar bone and using turned surface implants.

Our studies also show that the micro-movement/friction between the implant and abutment might also have a direct effect on osteolysis. The development of a microgap at the implant–crown interface can be a cause of tribocorrosion, reflected in the activation of ‘alarm’ proteins like IL-33. This points to an indirect and pathogenic effect of the titanium particles, causing an exacerbated pro-inflammatory response. A clinical approach would be to modulate the action of key factors like IL-8 and CCR7, preserving the integrity of the peri-implant tissue. However, there is, still, an insufficient knowledge of the immune microenvironment in peri-implantitis, and there are a few studies using coated or loaded implants with anti-inflammatory and/or bacteriostatic drugs: T-PRF, dexamethasone, and doxycycline. Regarding up-regulation of transcription factors like NLRP-3, our studies, reinforce its use as an immune biomarker. There are already studies being conducted using transcriptomic, proteomic, and epigenomic tools and single cell-sequencing characterising the inflammatory response that can help to identify prognostic biomarkers of PI and help to prevent implant failure [56–58].

4.2. Study Limitations

Regarding study limitations, PI is a pathological condition making it hard to compare in vitro and in vivo studies. The role of titanium particles relates to particle concentration and size parameters not standard in all the included studies. Until now most of the studies looked to cell viability and not cell proliferation/activation. Concerning in vitro studies, the design of the experiment is often focused on the immunological parameter without considering other factors like cell–bacteria interactions and the microbiome. The quality assessment of in vitro studies on dental materials is still under development; this was reflected by the medium score obtained in our studies—8 out of 14. The lack of standardised guidelines and methodological inconsistency are key factors that increase the risk of systematic errors. Overall, despite methodological heterogeneity, evidence quality remains acceptable. Also, the outcomes assessed vary with the detection methods, sample type (in vivo studies), and, more importantly, time. Furthermore, in vivo there is the small sample size and variations among individuals. All these limitations must be taken into account.

5. Conclusions

The immune system plays a crucial role in maintaining homeostasis, particularly during implant insertion. After implantation, it enables wound healing, prevents infection, and controls the inflammatory process underlying bone formation and resorption. Thus, excessive inflammation of the soft surrounding tissue can be exacerbated by titanium particle dissolution subsequent to bio-tribocorrosion, and leading to implant failure. It is thought that characterising the inflammatory response in PI, the cellular composition, cytokine secretion, and up-regulation of transcription factors may help in designing strategies for therapeutic approaches or for implant failure prevention, profiling risk patients, and immune biomarkers of PI.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/oral5040080/s1>, PRISMA Checklist, Table S1A. Risk of bias-Methodological evaluation of cross-sectional studies-Joanna Briggs Institute Critical Appraisal tools. Table S1B. Risk of bias-Methodological evaluation of case control studies-Joanna Briggs Institute Critical Appraisal tools; Table S2. Methodological evaluation In-vitro studies CONSORT modified.

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