

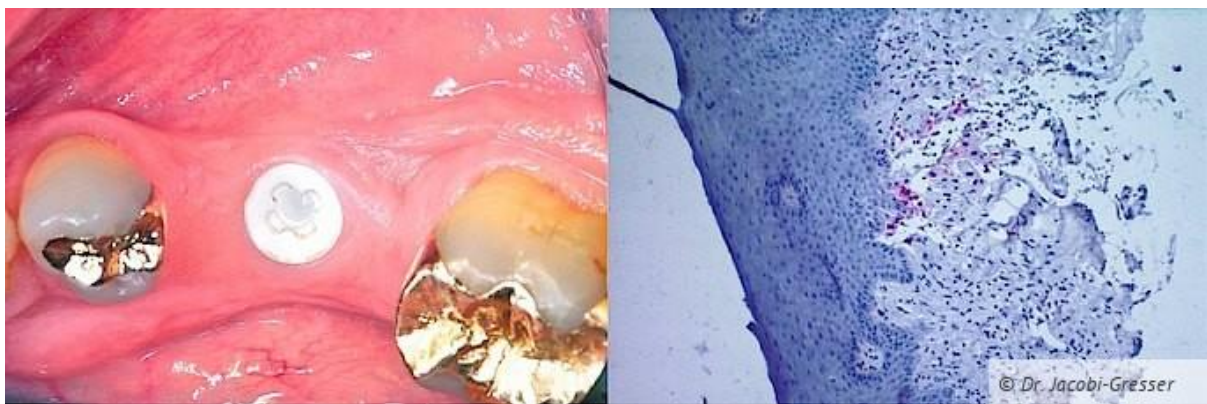
PERI-IMPLANTITIS

Pathogenesis of peri-implantitis

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Peri-implant mucosa around two-part screw-retained zirconium implant (ZERAMEX XT) in region 36. Histology of peri-implant mucosa around zirconium implant without inflammatory reaction.

In the 50-year history of oral implantology, we are increasingly confronted with inflammatory effects in peri-implant soft and hard tissue. This is partly due to the increasing use of dental implants, a wide range of indications and lack of attention to patient-related risk factors.

Whereas mucositis, in analogy to gingivitis, defines itself as a reversible inflammation of the peri-implant mucosa, peri-implantitis is characterized by an irreversibly progressive inflammatory process, in which not only the peri-implant soft tissue but also the surrounding bone is affected by destruction [1]. At the microscopic-molecular level, peri-implant tissues and physiological periodontium are different. The peri-implant tissue structures is more susceptible to inflammation due to less vascularization and altered, parallel collagen fibre orientation.

Since peri-implant osseointegration is considered to be an immunologically modulated interaction with the foreign implant material, marginal bone resorption implies the loss of foreign body equilibrium, i.e. loss of a well-balanced, balanced foreign body reaction [2]. The data on prevalence differs considerably in the literature: for peri-implant mucositis of up to 40-80% of implant patients and 20-50% of implants and for peri-implantitis of 10-56% resp. 10-40% [3]. Patients with a history of periodontitis and not permanently successful therapy are at increased risk of inflammation and consecutive implant loss. So far, the focus has been mainly on biofilm-associated risks.

Relevant Functional Polymorphisms (SNPs) in the IL-1, TNF-A and IL-1RA Gene		
Gene	Polymorphism	Effect
IL-1a	-889 C/T	Increased Release ↑
IL-1b	+3953 C/T	Increased Release ↑
TNF-a	-308 G/A	Increased Release ↑
IL-1RN	+2018 T/C	Decreased Release ↓

SNP – single nucleotide polymorphism

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Fig. 1: Functionally relevant polymorphisms on cytokine-producing genes that are associated with an increased inflammatory response.

IL1B +3953 C/T rs 1143634	MAF	global: caucasian: african american: asian:	14 % 20 % 13 % 5 %
IL1A -889 C/T rs 1800587	MAF	global: caucasian: african american: asian:	26 % 25 % 36 % 2,5 %
IL1RN +2018 T/C rs 419558	MAF	global: caucasian : african american: asian:	14 % 20 % 4 % 5 %
TNFA -308 G/A rs 1800629	MAF	global: caucasian : african american: asian:	10 % 17 % 15 % 3 %

MAF = minor allele frequency

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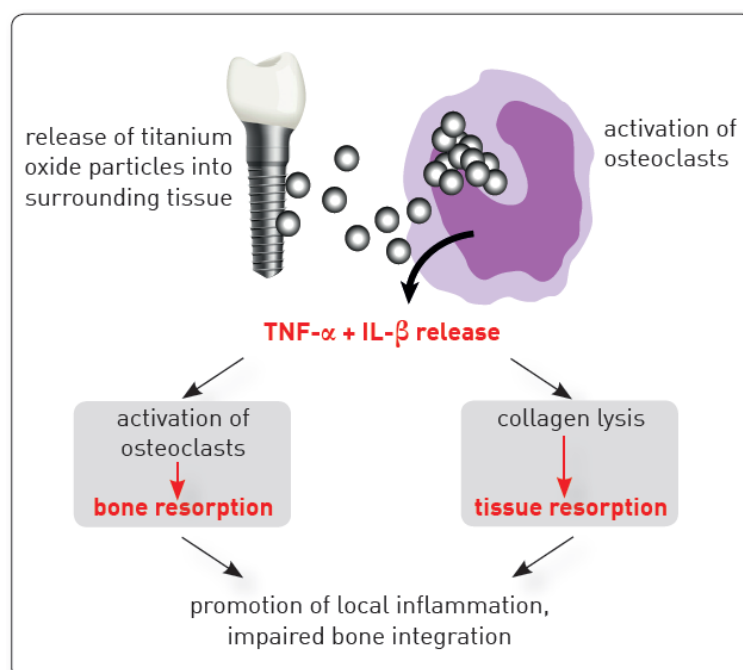
Fig. 2: The percentage distribution of polymorphisms to different ethnic groups.

Genetic risk factors for peri-implantitis

The close association of genetic variants with the severity of periodontitis has been confirmed by numerous studies. Due to a comprehensive data collection, meta-analyses are now available that have confirmed the importance of these cytokine polymorphisms in large groups of patients also for peri-implantitis and implant loss [4]. Patients with no or only one polymorphism on the cytokine-producing genes have normal inflammatory capacity. In contrast, patients who carry more than two of these genetic variants are called high responders because they are genetically determined to have a high degree of inflammation.

Analogous to periodontitis, the extent and course of the inflammatory response in peri-implantitis is also determined by the ratio of the pro- and anti-inflammatory cytokines IL-1 α and IL-1 β , TNF- α and IL-1RN. The clinical relevance of these polymorphisms is also demonstrated by the fact that patients with high responder polymorphisms for TNF- α and IL-1 also have an increased susceptibility to peri-implant bone loss in addition to the increased association with periodontitis [5- 9]. The concentration of inflammatory cytokines IL-1 and TNF- α in the affected periodontal area correlates with the severity of periodontitis [10]. The extent of tissue loss is increased in smokers with genetically increased risk [11]. Polymorphisms in the pro-inflammatory IL-6 gene and in the anti-inflammatory IL-10 gene may also be the cause of an excessive inflammatory response. The polymorphism -174G / C in the IL-6 gene is associated with increased IL-6 secretion. In studies on periodontitis, this genetic variant has been associated with chronic as well as aggressive disease processes [12].

Increased IL-6 expression has been shown to correlate with implant loss [13]. Interleukin-10 (IL-10) is another anti-inflammatory cytokine besides IL-1-RA. The polymorphism -592C / A in the IL-10 gene is associated with decreased IL-10 synthesis. The resulting reduced inhibition of inflammation explains why this genetic variant has been associated with periodontitis in many studies and has been confirmed in a meta-analysis as a predisposing factor for chronic periodontitis [14]. It has been shown that in affected patients the reduced IL-10 release results in significantly increased bone resorption and increased tissue destruction [15].



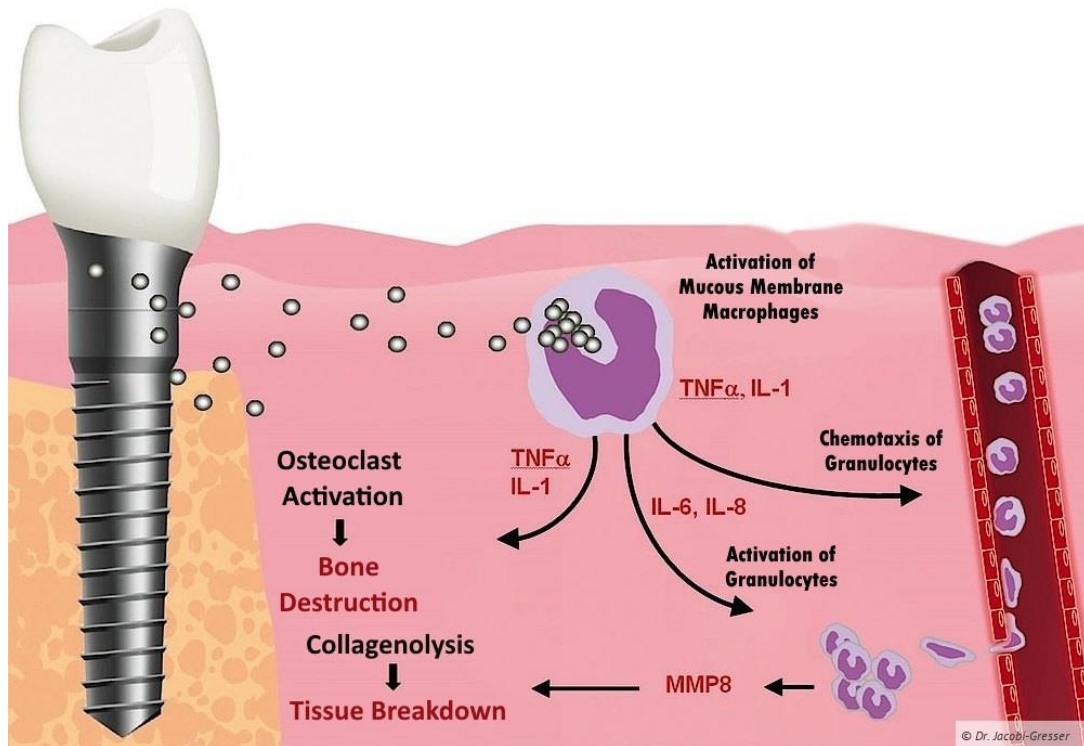


Fig. 3: Particle-activated macrophages release proinflammatory cytokines with local tissue effects.

Fig. 4: Activated macrophages activate an inflammatory cascade.

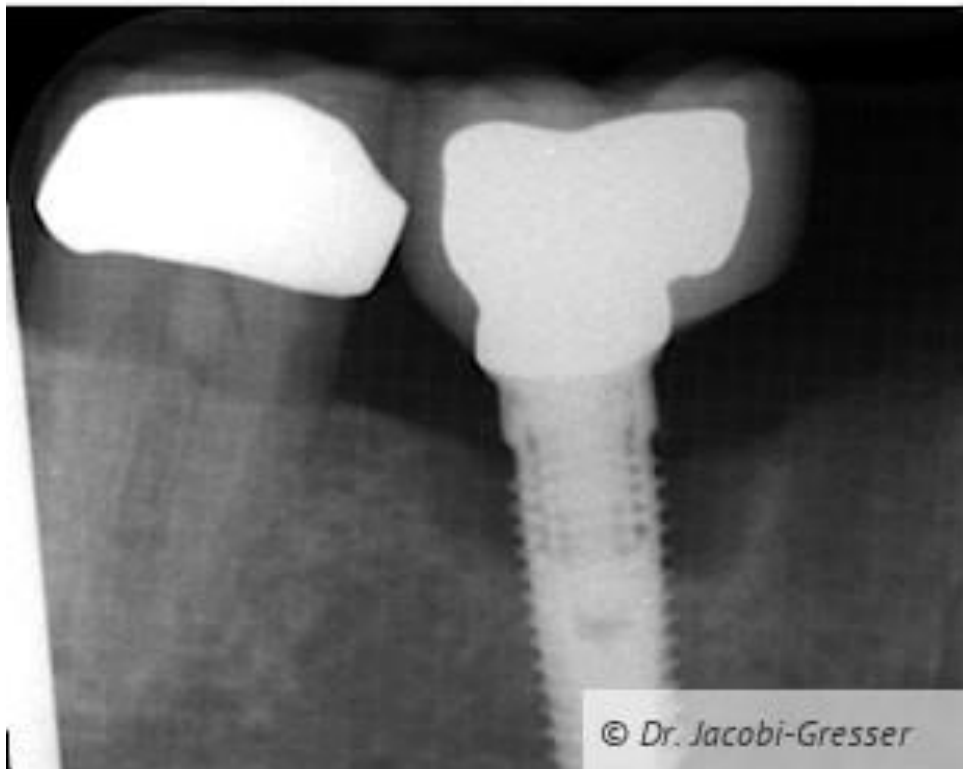


Fig. 5: Radiographic presentation of advanced peri-implantitis.



Fig. 6: Oral site in advanced peri-implantitis showing granulation tissue.

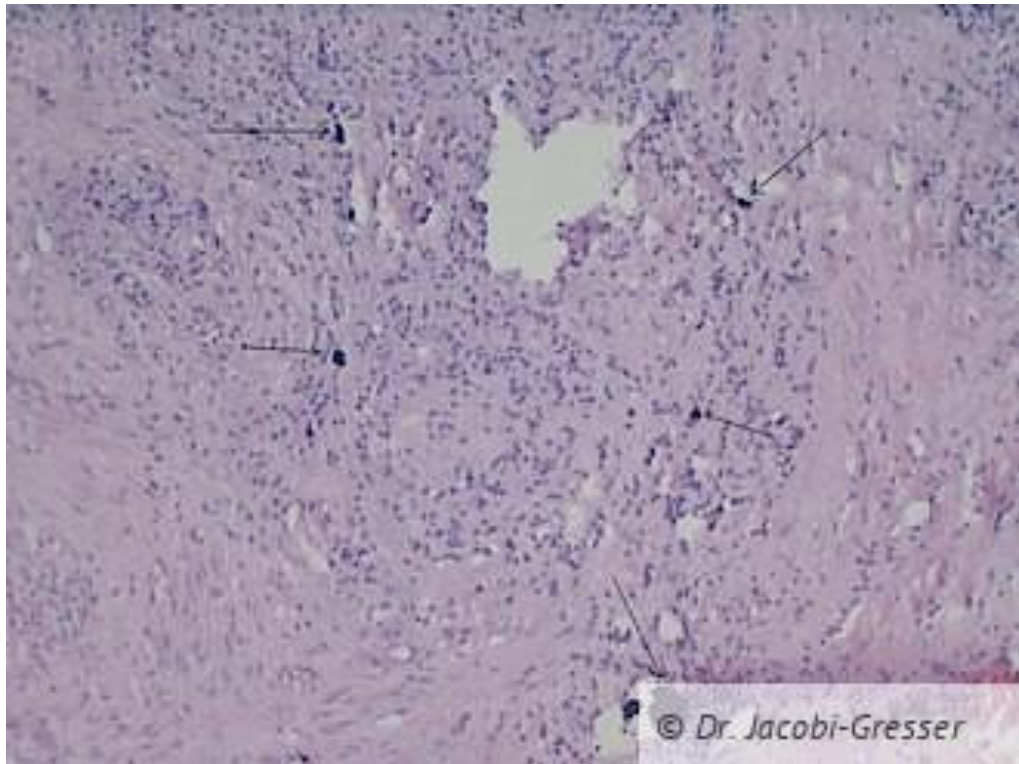


Fig. 7: Histology with pronounced granulomatous peri-implant inflammation with deposition of titanium particles (magnification x 100, Dr. W. Esinger).

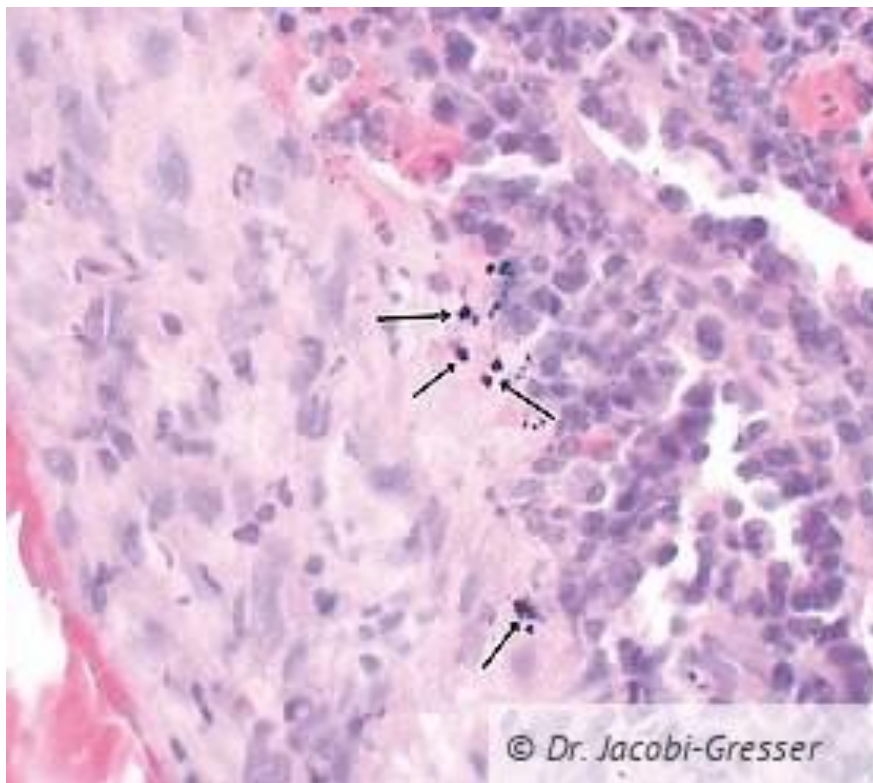


Fig. 8: Illustration of titanium microparticles surrounded by inflammatory cells (magnification x 200, Dr. W. Esinger).

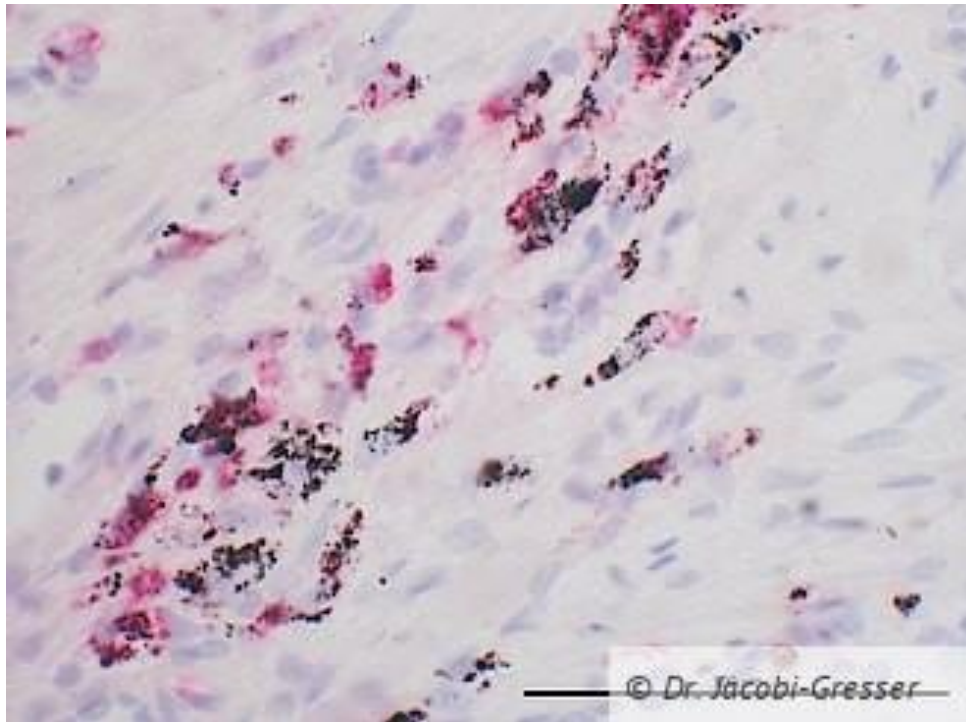


Fig. 9: CD 68 - Histoimmunfärbung to represent the macrophages. Titanium micro- and nanoparticles are found intra- and extracellularly by scavenger cells. (Magnification x 200, Dr. W. Esinger).

The individual risk of titanium implant-associated peri-implantitis is also due to a genetic susceptibility. The clinical effects of individual gene variants are moderate, so that - similar to other complex diseases - the presence of polymorphisms of several functional genes are involved in the development of peri-implantitis and/or implant loss [16].

Deficiency of mucosal resistance and granulocyte function

In about 10 percent of patients with chronic periodontitis is an inefficient pathogen defense in disturbed mucosal immunity - but no genetically induced increased tendency to inflammation - before. Here, defects of mucosal resistance may be responsible for aphthous ulcers but also for periodontitis and mucositis. As part of immunological defense, the periodontopathogenic bacteria are phagocytosed and killed by granulocytes. In rare cases congenital, but more often due to metabolic diseases (eg diabetes), the granulocyte function may be disturbed (Phagozytosedefekt). An additional reduction in granulocyte function may be due to lack of IgA antibodies or mannose-binding lectin (MBL), which improve the binding between granulocytes and bacteria required for effective elimination (opsonization). These parameters should be clarified above all if the corresponding inflammatory genetics does not indicate an excessive inflammatory tendency and thus the chronic inflammatory tendency cannot be genetically explained.

Titanium particle release by corrosion

However, scientific studies are now increasingly considering the special properties of the implant material and its surface morphology. As a very oxidation-friendly metal, titanium forms oxide layers on its surface in a physiological environment that lead to passivation and protect it from corrosion [17]. On the one hand, the roughness of the surface promotes osseointegration, on the other hand it also favors particle abrasion [18]. For two decades, the scientific focus has been directed to the effects of titanium particles, which detach themselves from the implant surface through mechanical abrasion during insertion and through corrosive events (bio-tribocorrosion) and cause immunological effects in the organism as micro- and nanoparticles [19,20]. , Titanium oxide particles show a significantly higher immunostimulatory potency compared to other oxide particles made of aluminum or zirconium ceramics [21]. Macrophages react after contact with titanium oxide particles with a release of the pro-inflammatory cytokines TNF- α and IL-1, which, among other things, leads to osteoclastic activation and, consequently, osteolysis in analogy to the pathogenesis of periodontitis [22].

Corrosion-promoting factors are mechanical, chemical and electrolytic nature (tribocorrosion).

Already the mechanical friction when inserting an implant as well as micro movements during the load lead to particle abrasion, the nanoscale thin oxide layer at the implant-bone interface and at the implant-abutment interface [23-25]. Compared with implant systems with and without platform switching, the latter showed higher particle loading in peri-implant tissue. The expression of the secreted cytokine levels was proportional to the tissue part load. In radiological control studies, the crestal bone level around platform-switching implants proved to be more stable [26]. Increased particle loading of the tissue surrounding the implant is also found after scaling measures on the implant surface [27]. The factors mentioned all lead to a particle dissemination in the surrounding and on the blood and lymphatic system in more distant tissues and organs. Mechanical abrasion and corrosive processes mutually reinforce each other. Scanning electron microscopy-energy dispersive spectroscopy (SEM-EDS) has been used to detect titanium nanoparticles (NPs) in the peri-implant bone of minipigs. The comparison of different implant surfaces revealed a different tissue load depending on features such as roughness and mechanical bond strength of the applied surface. Already on the day after the implant insertion into the jawbone of the test animals, particles in the peri-implant tissue were detectable. The authors conclude that over time, a critical particle loading in the peri-implant tissue may occur, resulting in damage to the osteoblasts [28].

Macrophage activation by particle release

Due to its outstanding oxidizing power unlike other metals, titanium generally has no allergenic potential because it is not present as an ion but as a particulate structure in tissues and therefore does not trigger a T-lymphocytic reaction under physiological conditions. Instead, the monocytic defense system is activated due to the particle stimulus [29, 30]. This process leads to the release of proinflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) by activation of monocytes / macrophages. In principle, the particle uptake by the macrophages leads to their activation. Due to the permanent release of particles, the inflammation-initiating stimulus persists, so that a sensitive organism is permanently triggered by a pro-inflammatory process. The pathomechanism of bone destruction by the proinflammatory cytokines TNF- α and IL-6 due to macrophage activation by titanium particles (MP, NP) from implants has been described [31]. The

extent of activation of human macrophages was measured in vitro and correlated with the extent of cytokine release found.

The formation of the cytokines TNF- α and IL-1 has not only local, but also systemic effects. As pro-inflammatory "alarm cytokines" they trigger complex immune reactions.

The increased defense response of tissue macrophages to particles is the underlying pathomechanism for a titanium particle-induced inflammatory response.

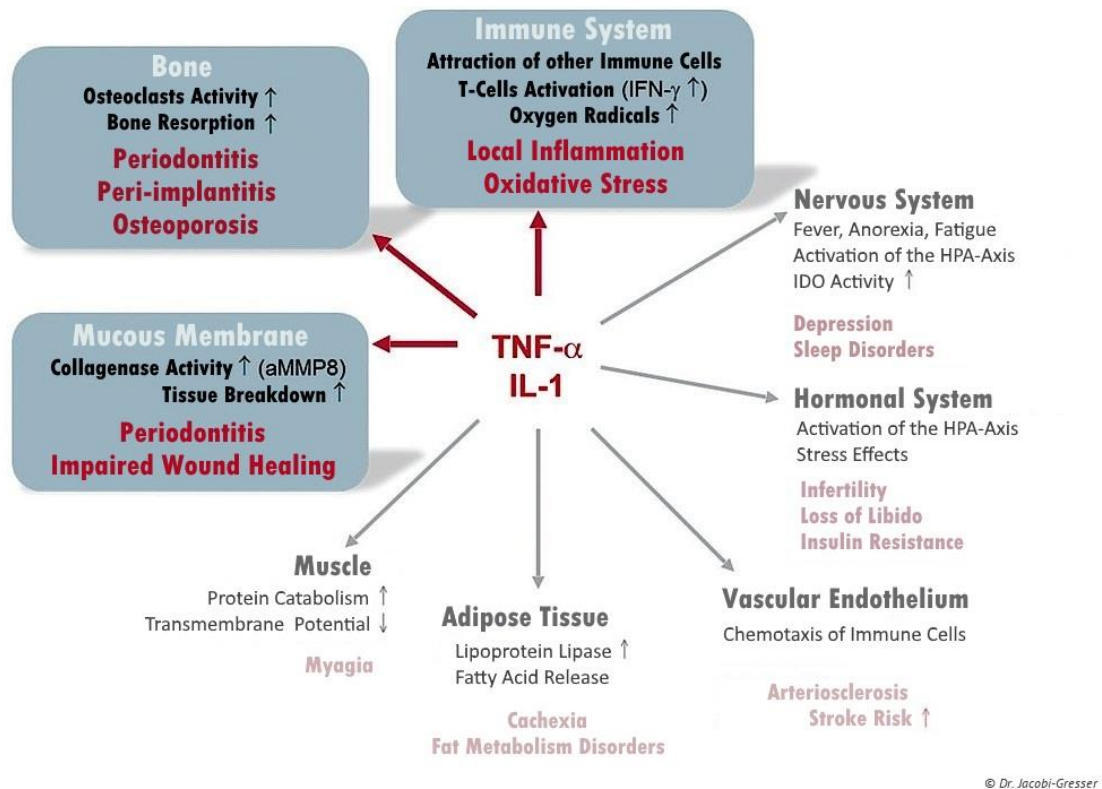


Fig. 10: The release of proinflammatory cytokines TNF- α and IL-1 β also has different systemic effects.

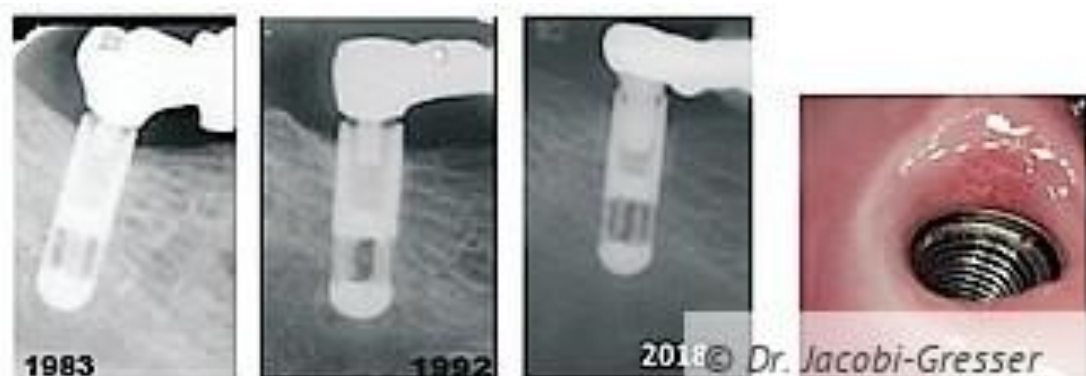


Fig. 11: Follow-up of a titanium implant of 36 years in a patient without inflammatory risk genetics. There is no bone loss.

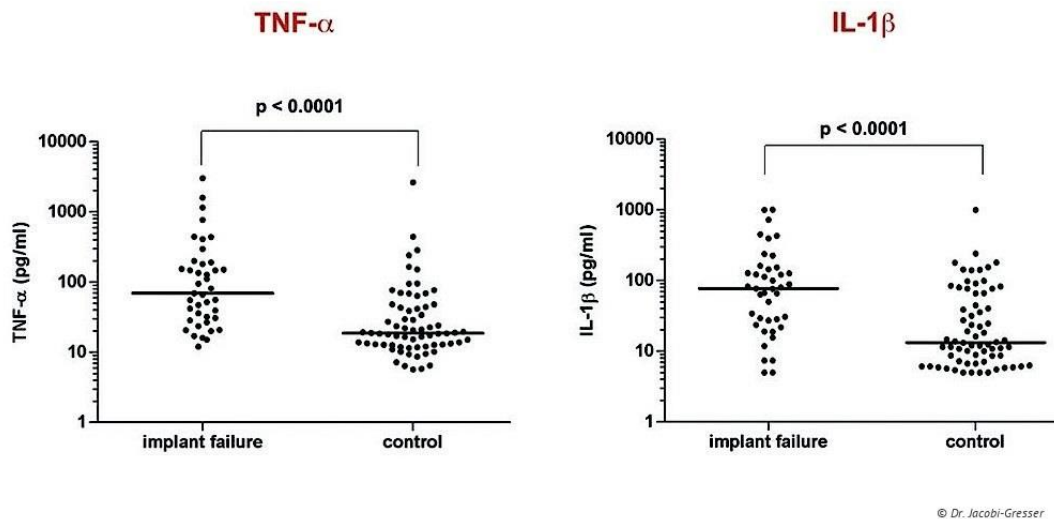


Fig. 12: Patients with increased secretion of proinflammatory cytokines *TNF-α* and *IL-1β* have a statistically significantly higher risk of implant loss (Jacobi-Gresser et al., 2013).

Microbial and particulate inflammasome activation

It has been shown that both periodontopathogenic bacteria and titanium oxide particles can independently activate the inflammasome cascade in the macrophages and thus stimulate cytokine production [32]. The activation of these inflammas leads to the formation of the pro-inflammatory cytokine *IL-1β*. In addition, biofilm adhesion to the titanium implant surface in turn promotes their corrosion processes [33]. A study on the association of proinflammatory synergisms of titanium NP / MP and *Porphyromonas gingivalis* (Pg) has shown that titanium nanoparticles without LPS (lipopolysaccharides) of Pg initiate a stronger inflammatory response than in combination with these bacteria due to their blocking influence on physiological osteoblast function [34, 35]. In a recent longitudinal study, the taxonomically different biofilm composition on implants compared to healthy teeth, but also in peri-implantitis and chronic-aggressive periodontitis using high-resolution gene sequencing (NGS) could be represented. It has been shown that the peri-implant microbiome in patients with chronic aggressive periodontitis differs substantially in its composition from the periodontitis of these periodontally affected patients. It is concluded that traditional periodontal therapy in peri-implantitis cannot be expected to achieve the same results, especially as further complex immunological mechanisms are involved [36]. *Staphylococcus aureus* is suspected to play an etiologically important role in peri-implantitis, especially since this germ has a high binding affinity to titanium surfaces and over half of all implants studied were populated [37]. Titanium nanoparticles also have far-reaching effects on bacterial growth by damaging their DNA structure [38]. It could be demonstrated that in comparison with zirconium particles with titanium particles of the same size and concentration, the latter have a significantly higher proinflammatory potential [39,40]. Some authors consider the use of zirconia as an implant material to prevent peri-implantitis due to the material-related lower biofilm adhesion. In vivo and in vitro studies demonstrate the reduced biofilm expression on the zirconium surface compared to that of titanium [41-44]. In general, biofilm accumulation is influenced by surface characteristics of the incorporated materials, such as their chemical composition, coating and roughness, and free surface energy [45,46]. Since the reactivity of the macrophages is a reaction of the nonspecific immune system, there is no need for prior exposure to the material as in sensitization developing after initial contact with the T-lymphocytic system. However, other strong pro-inflammatory influences, such as acute illnesses,

vaccinations, etc., also influence the current reactivity of the immune system. The intolerance to titanium is therefore not an allergy, but an unspecific inflammatory reaction (peri-implantitis)! Coating and its roughness and surface free energy [45,46]. Since the reactivity of the macrophages is a reaction of the nonspecific immune system, there is no need for prior exposure to the material as in sensitization developing after initial contact with the T-lymphocytic system. However, other strong pro-inflammatory influences, such as acute illnesses, vaccinations, etc., also influence the current reactivity of the immune system. The intolerance to titanium is therefore not an allergy, but an unspecific inflammatory reaction (peri-implantitis)! Coating and its roughness and surface free energy [45,46]. Since the reactivity of the macrophages is a reaction of the nonspecific immune system, there is no need for prior exposure to the material as in sensitization developing after initial contact with the T-lymphocytic system. However, other strong pro-inflammatory influences, such as acute illnesses, vaccinations, etc., also influence the current reactivity of the immune system. The intolerance to titanium is therefore not an allergy, but an unspecific inflammatory reaction (peri-implantitis)! There is no need for prior exposure to the material as in sensitization that develops after initial contact with the T-lymphocytic system. However, other strong pro-inflammatory influences, such as acute illnesses, vaccinations, etc., also influence the current reactivity of the immune system. The intolerance to titanium is therefore not an allergy, but an unspecific inflammatory reaction (peri-implantitis)! There is no need for prior exposure to the material as in sensitization that develops after initial contact with the T-lymphocytic system. However, other strong pro-inflammatory influences, such as acute illnesses, vaccinations, etc., also influence the current reactivity of the immune system. The intolerance to titanium is therefore not an allergy, but an unspecific inflammatory reaction (peri-implantitis)!

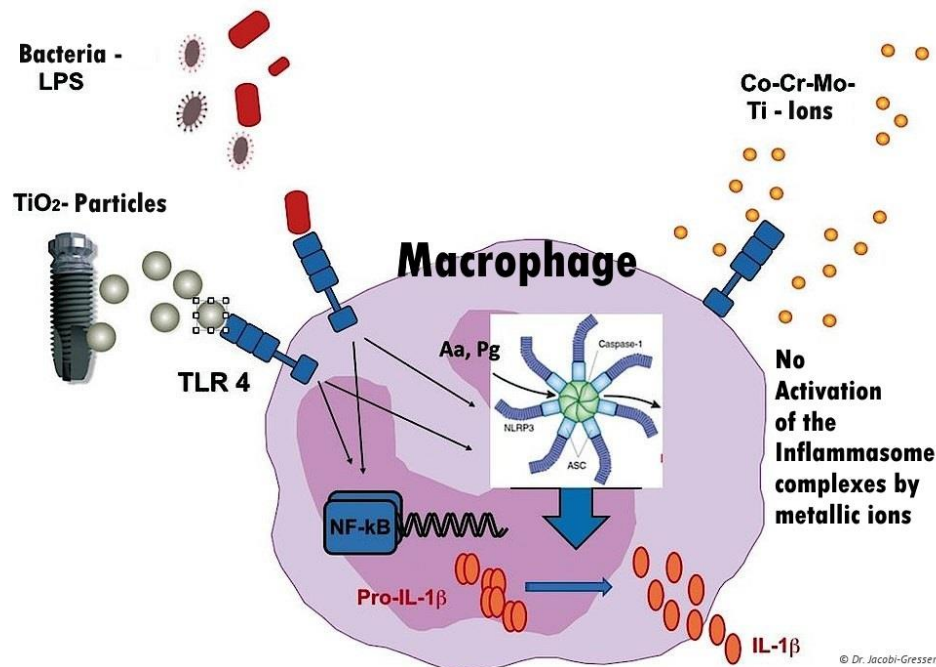


Fig. 13: Inflammasome activation in macrophages by periodontopathogens and by titanium particles via binding to toll-like receptors on the surface of immune cells. Particles unlike ions initiate the inflammatory cascade.

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But also, by corrosion or abrasion of metals from metallic dentures in general, and not only from implant restorations, metal ions reach the saliva in sometimes high concentrations [47]. These can cause toxic mucous membrane reactions or, in the case of existing allergic sensitization, even in a lower concentration cause periodontal / peri-implant inflammatory reactions. The inflammatory response does not have to be limited to the contact site, as is often assumed. The distributional function of saliva also reaches other mucous membrane areas of the oral cavity. In addition, periodontopathogenic pathogens play a catalyzing role in such material-induced inflammatory reactions. Of these, patients with an increased level of genetic inflammation are more affected.

Conclusion

Peri-implantitis is a pathogenetically complex clinical picture and, in addition to local effects, has systemic effects depending on individual genetic susceptibility. It has some similarities to periodontitis but differs in the taxonomic biofilm composition and is also involved in foreign body reactions to the implant material. Patients with a periodontitis history have a genetically higher risk of developing peri-implantitis. Pre-implantological risk diagnostics for appropriately scheduled patients allows for a differentiated implant-prosthetic procedure with the aim of avoiding peri-implantitis development. For early diagnosis and therapy monitoring, laboratory biomarkers such as calprotectin or the aMMP-8 determination from the sulcus fluid are now available to initiate anti-inflammatory measures at an early stage and to control their efficiency [48, 49]. An adapted to the patient monitoring in defined time intervals is indispensable due to individual risk burdening.

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