Current scientific status

Study overview

Ceramic-implantology | Interference fields of the oral cavity | Vitamins relevant for dentistry

TITANIUM IMPLANTOLOGY AND PERIIMPLANTITIS

2.1 Basic Research

2.2 Clinically relevant Studies and Papers

SWISS BIOHEALTH ACADEMY

CENTER HOČEVAR

1. TITANIUM IMPLANTOLOGY AND PERIIMPLANTITIS

2.1 Basic Research

INT J ORAL MAXILLOFAC SURG. 1994 DEC;23(6 PT 2):450-2.

Titanium deposition in regional lymph nodes after insertion of titanium screw implants in maxillofacial region.

Weingart D, Steinemann S, Schilli W, Strub JR, Hellerich U, Assenmacher J, Simpson J.

ABSTRACT

The deposition of titanium in regional lymph nodes was studied after insertion of endosseous, plasma-spray-coated titanium screw implants in a total of 19 beagle dogs. Five additional animals with no implants served as the control group. After killing the animals 9 months postoperatively, the regional lymph nodes were carefully excised, and samples were prepared for histologic examination. Other samples were used to identify foreign particles by energy-dispersive x-ray analysis and for measurement of the titanium concentration in the tissue by flameless atomic absorption spectroscopy. Very fine foreign-body particles could be seen in the histologic sections, and they were identified as titanium by energy-dispersive x-ray analysis. The atomic absorption analysis for titanium revealed a significantly higher concentration in the group with implants. The presence of very fine, poorly attached particles on the plasma-sprayed titanium surface suggests that these particles may be mechanically dislodged from the surface on insertion of the implants. This suggests that the fine particles may be transported by phagocytes to the regional lymph nodes, where they could be found without any signs of inflammation or foreign-body reaction.

J BONE JOINT SURG AM. 1999 MAY;81(5): 603-15.

Signaling pathways for tumor necrosis factor-alpha and interleukin-6 expression in human macrophages exposed to titanium-alloy particulate debris in vitro.

Nakashima Y, Sun DH, Trindade MC, Maloney WJ, Goodman SB, Schurman DJ, Smith RL.

ABSTRACT

BACKGROUND:

Loosening of the implant after total joint arthroplasty remains a serious problem. The activation of macrophages by wear debris from implants, mediated by the release of cytokines that elicit bone resorption, may lead to loosening. The purpose of the present study was to elucidate the mechanisms of macrophage activation by titanium particles from the components of implants and to identify the signaling pathways involved in particle-mediated release of cytokines.

METHODS:

Macrophages were isolated from mononuclear leukocytes obtained from healthy human donors and were exposed to titanium-alloy particles that had been obtained from periprosthetic membranes collected at revision total joint arthroplasties and then enzymatically prepared. The experimental protocols included examination of the effects of the inhibition of phagocytosis and the binding of antibodies to macrophage complement receptors on particle-induced macrophage activation. The release of the proinflammatory cytokines TNF-alpha (tumor necrosis factor-alpha) and IL-6 (interleukin-6) was used to assess macrophage activation. The signaling pathways involved in the induction of cytokine release were analyzed by identification of phosphorylated proteins with use of the Western blot technique and by translocation of the transcription factors nuclear factor-kappa B (NF-kappaB) and nuclear factor-interleukin-6 (NF-IL-6) into the nuclear protein fraction with use of electrophoretic mobility shift assays. The role of serine/threonine and tyrosine kinase pathways in the activation of nuclear factors and the release of cytokines was examined with use of selective pharmacological agents.

RESULTS:
Exposure of macrophages to titanium-alloy particles in vitro for forty-eight hours resulted in a fortyfold increase in the release of TNF-alpha and a sevenfold increase in the release of IL-6 ($p<0.01$). Phagocytosis of particles occurred in approximately 73 percent of the macrophages within one hour of exposure. Pretreatment of the macrophages with cytochalasin B reduced phagocytosis by 95 percent but did not reduce the release of TNF-alpha or IL-6. Thus, phagocytosis of particles was not necessary for induction of the release of TNF-alpha or IL-6 in the cultured macrophages. Ligation of the macrophage CD11b/CD18 receptors by integrin-specific antibodies also increased the release of TNF-alpha and IL-6. Antibodies to CD11b/ CD18 receptors (macrophage Mac-1 receptors) reduced phagocytosis of particles by 50 percent ($p<0.05$). (The CD11b/CD18 macrophage receptor is the macrophage receptor for the complement component CR3bi. The CD11b/CD18 macrophage receptor can also bind to ICAM-1 and ICAM-2. CD is the abbreviation for cluster of differentiation, and ICAM is the abbreviation for intercellular adhesion molecule.) Inhibition of phagocytosis was not accompanied by a decrease in the release of TNF-alpha and IL-6. Blocking RNA synthesis with actinomycin D or preventing protein synthesis with cycloheximide abolished or decreased particle-induced release of TNF-alpha and IL-6 from the macrophages. Macrophage release of TNF-alpha and IL-6 in response to particles coincided with increased tyrosine phosphorylation and mitogen-activated protein kinase activation. Inhibition of tyrosine and serine/threonine kinase activity decreased the particle-induced release of cytokines. Exposure of macrophages to either titanium-alloy particles or to antibodies to the receptor proteins CD11b and CD18 for thirty minutes activated the transcription factors NF-kappaB and NF-IL-6. Inhibition of particle phagocytosis did not block activation of the transcription factors. However, inhibition of tyrosine and serine/threonine kinase activity decreased the activation of NF-kappaB and NF-IL-6.

CONCLUSIONS:
These data suggest that particle induced macrophage release of TNF-alpha and IL-6 does not require phagocytosis but is dependent on tyrosine and serine/threonine kinase activity culminating in activation of the transcription factors NF-kappa B and NF-IL-6.

CLINICAL RELEVANCE:
Retrieval studies have documented numerous macrophages in association with particulate debris in granulomatous tissue surrounding failed total joint replacements. However, the molecular basis on which wear particles induce macrophage expression of proinflammatory cytokines and bone-resorbing factors remains unclear. This in vitro study showed that particles incite the release of proinflammatory cytokines from macrophages in the absence of phagocytosis. These results imply that contact of wear particles with macrophage cell-surface membrane proteins, such as the complement receptor CD11b/CD18, is sufficient signal for release of proinflammatory cytokines. The data further suggest that release of proinflammatory cytokines follows transmission of a membrane recognition event through intracellular signaling pathways that effect gene activation and protein synthesis. Therefore, these data indicate that a reduction in the formation of wear particles can be expected to improve the outcome after total joint arthroplasty by decreasing macrophage activation.

AUST DENT J. 2002 SEP;47(3):214-7.

A study of titanium release into body organs following the insertion of single threaded screw implants into the mandibles of sheep.

Frisken KW, Dandie GW, Lugowski S, Jordan G.

ABSTRACT

BACKGROUND:
Titanium is generally considered a safe metal to use in implantation but some studies have suggested that particulate titanium may cause health problems either at the site overlying the implant or in distant organs, particularly after frictional wear of a medical prosthesis. It was the purpose of this investigation to study the levels of dissemination of titanium from threaded screw type implants following placement of single implants in sheep mandibles.

METHOD:
Twelve sheep were implanted with a single 10x3.75mm self-tapping implant for time intervals of one, four and eight to 12 weeks. Four unoperated sheep served as controls. Regional lymph nodes, lungs, spleens and livers were dissected, frozen and subsequently analysed by Graphite Furnace Atomic Absorption Spectroscopy.

RESULTS:
Results associated with successful implants showed no statistically significant different levels of titanium in any organ compared to controls, although some minor elevations in titanium levels within the lungs and regional lymph nodes were noted. Two implants failed to integrate and these showed higher levels of titanium in the lungs (2.2-3.8 times the mean of the controls) and regional lymph nodes (7-9.4 times the levels in controls).

CONCLUSIONS:
Debris from a single implant insertion is at such a low level that it is unlikely to pose a health problem. Even though the number of failed implants was low, multiple failed implants may result in considerably more titanium release which can track through the regional lymph nodes. Results suggest that sheep would be an excellent model for following biological changes associated with successful and failed implants and the effect this may have on titanium release.

IMPLANT DENT. 2003;12(1):75-80.

Macrophages related to dental implant failure.

Olmedo D, Fernández MM, Guglielmotti MB, Cabrini RL.

ABSTRACT

PURPOSE:
The aim of this study was to evaluate, histologically and quantitatively, the presence of macrophages loaded with metallic particles in the periimplant soft tissues of failed titanium (Ti) dental implants.

MATERIALS AND METHODS::
The study was performed on sections of metallic Ti implants embedded in methyl methacrylate resin that exhibited macrophages in the soft tissues contiguous with the implant. The volume of periimplant soft tissue was evaluated, and the number of macrophages was determined. The particles within macrophages were analyzed by energy-dispersive x-ray analysis.

RESULTS:
Macrophages were more abundant in the zone adjacent to the metallic implant as compared with the zone further away from the implant. Energy-dispersive x-ray analysis revealed the presence of Ti within macrophages.

CONCLUSIONS:
Macrophages loaded with Ti particles can be associated with a corrosion process. The method proposed would allow for the objective evaluation of the presence of macrophages associated with dental implants and other orthopedic materials that contain Ti or other metals.

DENT MATER. 2003 JAN;19(1):54-9.

Galvanic corrosion behavior of implant suprastructure dental alloys.

Taher NM, Al Jabab AS.

ABSTRACT

OBJECTIVE:

The purpose of this study was to evaluate and compare in vitro, the galvanic corrosion behavior of Co-Cr alloys (R2000, R800), Ni-Cr (RCS), silver-palladium (Jelstar), Gold (Pontallor-4) and Ternary Ti (experimental Ter Ti) when coupled with endosseous Ti implant abutment material. Amalgam alloy and commercially pure Ti cylinders (SSTi) were coupled with endosseous Ti implants as negative and positive controls, respectively.

METHODS:

An EG&G Model 263 Scanning Potentiostat was used for this purpose. Specimens were prepared and fresh artificial saliva was used as an electrolyte solution. The experiment run time was 24h for each couple. The common potential, galvanic current and current integration during the last 6h were recorded for each couple.

RESULTS:

The results showed that the best couples were Ti/Pontallor-4, Ti/Ter Ti, Ti/R800 and Ti/Jelstar. The least acceptable couples were Ti/amalgam, SSTi/SSTi and Ti/R2000, while the Ti/RCS couple showed unstable galvanic corrosion behavior.

SIGNIFICANCE:

It is concluded that the following alloys can be used as suprastructure alloys with Ti implants: Pontallor-4, R800, Jelstar and Ter Ti. Although Ter Ti alloy is an experimental alloy, it showed good results, but cannot be used in the clinical field unless extensive investigations are carried out. The SSTi/SSTi couple showed unexpected galvanic corrosion behavior which needs further investigation.

BIOMED TECH (BERL). 2004 DEC;49(12):340-4.

Effects of clinically relevant alumina ceramic, zirconia ceramic and titanium particles of different sizes and concentrations on TNF-alpha release in a human macrophage cell line

Sterner T, Schütze N, Saxler G, Jakob F, Rader CP.

ABSTRACT

INTRODUCTION:

Aseptic loosening is considered to be the main problem of modern endoprothesis. Tumor necrosis factor alpha (TNFalpha) seems to be the initiator protein of particle disease. The aim of our study was to investigate the TNFalpha response of macrophage like cells (MLC) after stimulation with periprosthetic particles, typically found during revision surgery. For this purpose alumina ceramic (Al2O3), zirconia ceramic (ZrO2) and titanium (Ti) particles of different sizes and concentrations were used. Important was to study the effects of different sizes due to TNFalpha secretion and the comparison of the biological effects of alumina ceramic and titanium.

METHOD:

To obtain an TNFalpha profile we used an established macrophage model (Rader et al.) with THP-1 cells (human monocytic cell line). Therefore 106 MLC were incubated with different particle concentrations and sizes for 6 h. The supernatant was then investigated for TNF using ELISA assay.

RESULTS:

Ti-particles provoked in both sizes (0.2 microm and 2.5 microm) the greatest TNFalpha response, 8 times and 17 times as high in comparison with control. But substantially more 0.2 microm sized Ti-particles were necessary to get the above mentioned results. Al2O3-particles were not as effective as Ti, but they released fourfold more TNFalpha compared to control. There was no difference in TNFalpha-secretion comparing Al2O3-particles of different sizes (0.6 microm and 2 microm), but a 1000 times greater concentration of the 0.6 microm sized particles were needed. Using Al2O3- and Ti-particles of the same size and concentration, Ti provoked a significant higher TNFalpha response. ZrO2 showed no effects on TNFalpha release.

CONCLUSION:

Because of our results we recommend ceramic articulating surfaces, which are superior to metal on metal matings ion term of biological reactions. Additionally bigger wear particles should be avoided. Revisionoperation should be done early to avoid huge amount of wear particles and to minimize local osteolysis.

WILEY PERIODICALS, INC. J BIOMED MATER RES, 2007.
HTTPS://DOI.ORG/10.1002/JBM.A.31514

Biological response of tissues with macrophagic activity to titanium dioxide

Olmedo DG, Tasat DR, Evelson P, Guglielmotti MB, Cabrini RL

ABSTRACT
The titanium dioxide layer is composed mainly of anatase and rutile. This layer is prone to break, releasing particles to the milieu. Therefore, corrosion may cause implant failure and body contamination. We have previously shown that commercial anatase–titanium dioxide (TiO2–anatase) is deposited in organs with macrophagic activity, transported in the blood by phagocytic-mononuclear cells, and induces an increase in the production of reactive oxygen species (ROS). In this study, we evaluated the effects of rutile–titanium dioxide (TiO2–rutile). Male Wistar rats were injected i.p. with a suspension of TiO2–rutile powder at a dose of 1.60 g/100 g b.w. Six months postinjection, the presence of Ti was assessed in serum, blood cells, liver, spleen, and lung. Titanium was found in phagocytic mononuclear cells, serum, and in the parenchyma of all the organs tested. TiO2–rutile generated a rise in the percentage of reactive cells, which was smaller than that observed when TiO2–anatase was employed in a previous study. Although TiO2–rutile provoked an augmentation of ROS, it failed to induce damage to membrane lipids, possibly due to an adaptive response. The present study reveals that TiO2–rutile is less bioreactive than TiO2–anatase.

INT J ORAL MAXILLOFAC SURG. 2008 NOV;37(11):1032-8. DOI: 10.1016/J.IJOM.2008.05.013. EPUB 2008 JUL 7.

Local effect of titanium implant corrosion: an experimental study in rats.

Olmedo DG, Duffó G, Cabrini RL, Guglielmotti MB.

ABSTRACT
The aim of this study was to evaluate histologically the biological effect of pitting corrosion and to contribute clinically relevant data on the permanence of titanium metal structures used in osteosynthesis in the body. Commercially pure titanium laminar implants (control) and commercially pure titanium laminar implants with pitting corrosion (experimental) were implanted in the tibiae of rats. At 14 days post-implantation the animals were killed. The tibiae were resected, fixed, radiographed and processed for embedding in methyl methacrylate. Percentage of bone-implant contact and peri-implant bone volume were evaluated. The histological study of the titanium implants submitted to pitting corrosion showed scarce bone-implant contact, it was only present in the areas with no pitting and/or surface alterations. There was a statistically significant lower percentage of bone-implant contact in the experimental group (6 %+/-4) than in the control group (26 %+/-6) ($p<0.001$). Products of corrosion in the peri-implant bed, especially around the blood vessels and areas of bone marrow in the metal-tissue interface, were observed. The microchemical analysis of corrosion products revealed the presence of titanium. The adverse local effects caused by pitting corrosion suggest that titanium plates and grids should be used with caution as permanent fixation structures.

J MATER SCI MATER MED. 2008 SEP;19(9):3049-56. DOI: 10.1007/S10856-008-3438-X. EPUB 2008 APR 4.

Biodistribution of titanium dioxide from biologic compartments.

Olmedo DG, Tasat DR, Guglielmotti MB, Cabrini RL.

ABSTRACT

The layer of titanium dioxide (TiO(2)) of the implant is chronically exposed to the internal electrolyte milieu in the peri-implant biological compartment. Corrosion results from electrochemical attack and ensuing gradual degradation of the metallic materials and is thus of biological interest when these biomaterials are employed in clinical implantology. Herein we evaluated and compared the chronic effect and the biodistribution of TiO(2) administered subcutaneously or intraperitoneally. We propose that the compartmentalization of titanium in the area of subcutaneous injection would reproduce the biological compartment of the implant and its microenvironment from which metal ions could be released and migrate systemically. Potential TiO(2) deposits were identified and characterized in skin, liver and lung by histological and EDX analyses. After both treatments, the skin, liver, and lungs exhibited histological evidence of TiO(2) deposits. In order to characterize in situ macrophage-like cells, tissue sections were immunohistochemically stained for CD68. Tissue specimens from all organs assayed showed positive staining for anti-macrophage monoclonal antibody CD68 (PGM1). Despite the compartmentalization of titanium within nodular areas in rats treated subcutaneously, systemic migration occurred. We concluded that systemic migration of TiO(2) occurred regardless of the administration route.

J BIOMED MATER RES A. 2009 OCT;91(1): 29-36. DOI: 10.1002/JBM.A.32183.

Titanium IV ions induced human osteoclast differentiation and enhanced bone resorption in vitro.

Cadosch D, Chan E, Gautschi OP, Meagher J, Zellweger R, Filgueira L.

ABSTRACT

There is increasing evidence that titanium (Ti) ions are released from orthopedic implants, with concentrations in the range of 1 microM in tissue and blood, and may play a role in aseptic loosening of orthopedic implants. This study investigated whether Ti(IV) ions induce differentiation of monocytic osteoclast precursors into osteoresorptive multinucleated cells and influence the activation and function of in vitro generated osteoclasts. Human monocytes and in vitro generated osteoclasts were exposed to 1 microM Ti(IV) ions for 10 days. Thereafter, osteoclast differentiation, activation, and function were evaluated. Transcription of specific osteoclastic genes was measured using quantitative reverse transcription polymerase chain reactions, which showed increased expression of tartrate-resistant acid phosphatase (TRAP) in approximately 20 % of Ti(IV)-treated monocytes. Detection and quantification of intracellular TRAP activity using ELF97 as a fluorescent substrate revealed a significant increase of TRAP-positive cells in Ti(IV)-treated monocytes. Additionally, as demonstrated on dentin slide cultures, Ti(IV)-treated monocytes became functional bone resorbing cells, significantly increasing their osteo-resorptive activity to similar levels as osteoclasts in vitro. These results suggest that Ti(IV) ions released by biocorrosion from orthopedic implants induce differentiation of monocytes toward mature, functional osteoclasts, which may well contribute the pathomechanism of aseptic loosening.

J NEUROSCI METHODS. 2009 MAR 30;178(1):182-7. DOI: 10.1016/J.JNEUMETH.2008.12.008. EPUB 2008 DEC 14.

Uptake and intracellular distribution of various metal ions in human monocyte-derived dendritic cells detected by Newport Green DCF diacetate ester.

Cadosch D, Meagher J, Gautschi OP, Filgueira L.

ABSTRACT

BACKGROUND:

The attempt to visualise intracellular protein metal complexes has currently been difficult due to the unavailability of probes for such molecular structures. Newport Green DCF diacetate ester is a cell permeant acetate ester, which b comes fluorescent after hydrolysis. This molecule is initially uncharged, allowing it to pass through cell membranes. Once in the cell, it is hydrolysed and becomes charged, hindering its escape from the cell and allowing it to bind charged protein metal complexes, which then become fluorescent.

METHODS:

In this study, we exposed cultured human monocyte-derived dendritic cells (mDC) to a variety of metal ions with the aim of having the cells take up and process protein metal complexes. Newport Green DCF diacetate ester was used to fluorescently label intracellular protein metal complexes.

RESULTS:

Flow cytometry analysis and confocal imaging showed specific staining for mDC exposed to aluminium, chromium, nickel, titanium and zirconium ions. The intensity of staining varied between ion types, whereby Ti(III) resulted in the brightest fluorescence signal. Aluminium, Cr(III), Ni, Ti(IV) and Zr(IV) were also clearly detectable.

CONCLUSION:

For the first time, intracellular metal ion protein complexes undergoing cellular processing were successfully visualised in human mDC using flow cytometry and confocal microscopy.

BULL NYU HOSP JT DIS. 2009;67(2):182-8.

Biologic effects of implant debris.

Hallab NJ, Jacobs JJ.

ABSTRACT

Biologic response to orthopedic implants debris is central to clinical performance. Eventual implant loosening due to aseptic osteolysis has been attributed to local inflammatory responses to wear and corrosion products that are produced by articulating implant interfaces. The response to implant debris is dominated by local immune activation, e.g. macrophages. Immune reactivity has been shown to depend on the number of particles produced or the dose (i.e., the concentration of phagocytosable particles per tissue volume, which can be characterized by knowing the size distribution and amount of debris). Elongated particles (fbers) are generally more pro-inflammatory than round particles, and there is a growing consensus that metals particles are more proinflammatory than polymers in vivo. Generally, to produce an in vitro inflammatory response, particles need to be less than 10 mum, i.e. phagocytosable. However, both soluble and particulate debris derived from Co-Cr-Mo alloy implants can induce monocyte/macrophage activation and secretion of pro-inflammatory cytokines such as IL-1beta, TNFalpha, IL-6 and IL-8 via up-regulation of transcription factor NFkappabeta, and activation of inflammasome danger signaling in human macrophages. Not only does activation of local (and systemic) inflammation result in decreased osteoblast function but osteoclast activity increases. Some people are more predisposed to implant debris induced inflammation and metal "allergy" testing services are becoming available. New pathways of implant debris-induced inflammatory reactions continue to be discovered, such as the "danger signaling" inflammasome pathway, which provides new targets for pharmaceutical intervention and improved implant performance.

J BIOMED MATER RES A. 2010 DEC 15;95(4):1004-10. DOI: 10.1002/JBM.A.32914. EPUB 2010 SEP 24.

Biocorrosion and uptake of titanium by human osteoclasts.

Cadosch D, Al-Mushaiqri MS, Gautschi OP, Meagher J, Simmen HP, Filgueira L.

ABSTRACT

All metals in contact with a biological system undergo corrosion through an electrochemical redox reaction. This study investigated whether human osteoclasts (OC) are able to grow on titanium and aluminum, and directly corrode the metals leading to the release of corresponding metal ions, which are believed to cause inflammatory reactions and activate osteoclastic differentiation. Scanning electron microscopy analysis demonstrated long-term viable OC cultures on the surface of titanium and aluminum foils. Atomic emission spectrometry investigations showed significantly increased levels of aluminum in the supernatant of OC cultured on aluminum; however, all measurements in the supernatants of cell cultures on titanium were below detection limits. Despite this, confocal microscopy analysis with Newport Green DCF diacetate ester staining depicted intense fluorescence throughout the cytoplasm and nucleolus of OC cultured on titanium foils. Comparable fluorescence intensities were not observed in monocytes and control cells cultured on glass. The present study demonstrated that human osteoclast precursors are able to grow and differentiate toward mature OC on titanium and aluminum. Furthermore, it established that the mature cells are able to directly corrode the metal surface and take up corresponding metal ions, which subsequently may be released and thereby induce the formation of osteolytic lesions in the periprosthetic bone, contributing to the loosening of the implant.

J BIOMED MATER RES A. 2010 FEB;92(2): 475-83. DOI: 10.1002/JBM.A.32390.

Titanium induced production of chemokines CCL17/TARC and CCL22/MDC in human osteoclasts and osteoblasts.

Cadosch D, Gautschi OP, Chan E, Simmen HP, Filgueira L.

ABSTRACT

There is increasing evidence that titanium (Ti(IV)) ions are released from orthopedic implants and play a role in aseptic loosening. This study aimed to investigate whether titanium induces expression of chemokines and cytokines that are important in osteoclastogenesis in human osteoclasts and osteoblasts. Incubation of those cells with 1 muM Ti(IV) significantly upregulated expression of CCL17/TARC and CCL22/MDC, RANK-L, M-CSF and pro-inflammatory cytokines as determined by quantitative real-time PCR and ELISA assays. Additionally, flow cytometry was used to show Ti(IV) related increased expression of CCR4, the cognate receptor for CCL17 and CCL22 in challenged osteoclast precursors. These results strongly suggest that Ti(IV) ions play a role in the recruitment of osteoclast precursors to the bone-implant interface by increasing CCL17 and CCL22 expression and by upregulating their cognate receptor. Moreover the increased expression of RANK-L and M-CSF by osteoblasts together with increased levels of pro-inflammatory cytokines may enhance osteoclast differentiation and activity, and subsequently contribute to the pathomechanism of aseptic loosening.

J ORTHOP RES. 2010 MAR;28(3):341-7. DOI: 10.1002/JOR.21013.

Titanium uptake, induction of RANK-L expression, and enhanced proliferation of human T-lymphocytes.

Cadosch D, Sutanto M, Chan E, Mhawi A, Gautschi OP, von Katterfeld B, Simmen HP, Filgueira L.

ABSTRACT

There is increasing evidence that titanium ions are released from orthopedic implants by biocorrosion. The aim of this study was to investigate titanium uptake by human T-lymphocytes and its effects on phenotype and proliferation. Freshly isolated human nonadherent peripheral blood mononuclear cells (NA-PBMC), were exposed to TiCl4 [Ti(IV)]. Bioavailability and distribution of Ti(IV) in T-lymphocytes was determined by energy-filtered electron microscopy (EFTEM). The effects of Ti(IV) challenge on nonactivated and PHA-activated cells were assessed by flow cytometric analysis of surface markers, RANK-L production, and proliferation assays. EFTEM colocalized Ti(IV) with phosphorus in the nucleus, ribosomes, cytoplasmic membranes, and the surface membrane of T-lymphocytes. Ti(IV) increased significantly the expression of CD69, CCR4, and RANK-L in a concentration-dependent manner. Titanium enters T-lymphocytes through a currently unknown mechanism and binds to phosphorus-rich cell structures. Titanium influences phenotype and function of T-lymphocytes, resulting in activation of a CD69+ and CCR4+ T-lymphocyte population and secretion of RANK-L. These results strongly suggest the involvement of titanium ions challenged T-lymphocytes in the complex pathophysiological mechanisms of aseptic loosening of orthopedic implants.

ZWR 2010; 119(5): 222-232. DOI: 10.1055/S-0030-1261273

Hyperreaktivität von Gewebemakrophagen nach Kontakt mit Titanoxidpartikeln als Ursache einer verstärkten lokalen Entzündungsreaktion bei Patienten mit Periimplantitis

Hyperactivity of Tissue-macrophages after Contact with Particles of Oxidated Titan as the Cause of an Enhanced Local Inflammatory Reaction in Patients with Periimplantitis.

Schütt S, Von Baehr V.

ABSTRACT

One of the main reasons for the high immunological tolerance of Titan in comparence to other metals is its excellent corrosive behaviour. On the other side it is well known by orthopedists and dentists that in some patients titanium implants induce inflammatory reactions that not seldom cause the integration of the implant to fail.

Until today the responsible mechanisms of this „titanium sensibilisation“ are only partially known. Contrary to allergies towards other metals, real cellular induced allergies for titan are very seldom. Due to their high affinity to oxygen, titan-ions directly after their release form oxides. Other than free ions, oxides can not bind to proteins en therefore can not act as a hapten.

A common cause of this „titanium sensibilisation“ is the exaggerated pro-inflammatory reactivity of tissue-macrophages after contact with titan(oxid)particles. This reaction is as well in vivo as in vitro measurable by the pro-inflammatory key-cytokines interleucine-1 and TNF-α. The cytokine response is not caused by the presence of specific lymphocytes but is based upon an enhanced inflammatory readiness of unspecific inflammatory cells after contact with debris (titan-particle-abrasion). The intensity of the inflammatory reaction of tissue-macrophages towards titan-particle-abrasion is mainly dependant upon genetical factors.

J ORAL PATHOL MED. 2011 MAY;40(5):412-20. DOI: 10.1111/J.1600-0714.2010.00958.X. EPUB 2010 OCT 24.

Mapping of titanium particles in peri-implant oral mucosa by laser ablation inductively coupled plasma mass spectrometry and high-resolution optical darkfield microscopy.

Flatebø RS, Høl PJ, Leknes KN, Kosler J, Lie SA, Gjerdet NR.

ABSTRACT

The present study examines the quantity, size, element signatures and distribution of titanium particles in normal oral mucosal tissue and in oral mucosa exposed to a titanium implant. Tissue samples from six healthy patients were obtained by a full thickness biopsy taken from the edge of the oral mucosa when inserting a titanium dental implant. At the abutment insertion 6 months later, a punch test biopsy of oral mucosa was taken over the implant site. Laser Ablation Inductively Coupled Plasma Mass Spectrometry (LA-ICP-MS) is a sensitive and specific multi-element microanalytical technique that demonstrated the presence of Ti particles in the tissue adjacent to implant cover-screws. The epithelial part of the control samples revealed more particles than the corresponding area of the test samples, consisting partly of newly formed scar tissue. High-Resolution Optical Darkfield Microscope (HR-ODM) confirmed the presence of particles in both the control and the test samples. The combination of LA-ICP-MS and HR-ODM appears to be a powerful combination for detection of particles in oral tissues; optical microscopy provides an overview with histological references, whereas LA-ICP-MS identifies the chemical composition.

J BIOMED MATER RES A. 2011 DEC 15;99(4):630-7. DOI: 10.1002/JBM.A.33222. EPUB 2011 SEP 27.

Macrophage response to high number of titanium particles is cytotoxic and COX-2 mediated and it is not affected by the particle's endotoxin content or the cleaning treatment.

Schwab LP, Marlar J, Hasty KA, Smith RA.

ABSTRACT

Periprosthetic osteolysis is a progressive deterioration of bone around prostheses resulting primarily from the presence of wear debris. Particulate material, number, and their interactions with environmental factors play important roles in macrophage activation around implants. We have previously shown that macrophages cultured in the presence of high numbers of cleaned titanium (Ti) particles released significant amounts of PGE_2 that is potentially detrimental for bone. Cleaning of particles has become routine in most studies of macrophage/particle interactions as contaminating endotoxin elicits a macrophage cytokine response and since numerous studies have suggested that endotoxins may be present on implant materials. However, the strenuous cleaning procedure itself represents a possible source of other contaminants (such as material by-products) that may be relevant to the prostanoid response of macrophages. To analyze this hypothesis, the macrophage response to high numbers of cleaned Ti particles was compared to that of unclean particles and to particles that were subjected to a short version of the cleaning procedure. It was found that neither the high amount of endotoxin on the unclean particles nor the duration of the cleaning procedure had an effect on the release of PGE_2 and the decrease in cell viability in response to high number of Ti particles. Evidence of a possible relationship between these two variables is presented.

J R SOC INTERFACE. 2012 NOV 7;9(76):3161-4. EPUB 2012 JUL 25.

Do 'passive' medical titanium surfaces deteriorate in service in the absence of wear?

Addison O, Davenport AJ, Newport RJ, Kalra S, Monir M, Mosselmans JF, Proops D, Martin RA.

ABSTRACT

Globally, more than 1000 tonnes of titanium (Ti) is implanted into patients in the form of biomedical devices on an annual basis. Ti is perceived to be 'biocompatible' owing to the presence of a robust passive oxide film (approx. 4 nm thick) at the metal surface. However, surface deterioration can lead to the release of Ti ions, and particles can arise as the result of wear and/or corrosion processes. This surface deterioration can result in peri-implant inflammation, leading to the premature loss of the implanted device or the requirement for surgical revision. Soft tissues surrounding commercially pure cranial anchorage devices (bone-anchored hearing aid) were investigated using synchrotron X-ray micro-fluorescence spectroscopy and X-ray absorption near edge structure. Here, we present the first experimental evidence that minimal load-bearing Ti implants, which are not subjected to macroscopic wear processes, can release Ti debris into the surrounding soft tissue. As such debris has been shown to be pro-inflammatory, we propose that such distributions of Ti are likely to effect to the service life of the device.

J PERIODONTOL. 2012 AUG;83(8):973-80. DOI: 10.1902/JOP.2011.110392. EPUB 2011 DEC 5.

Oral mucosa tissue response to titanium cover screws.

Olmedo DG, Paparella ML, Spielberg M, Brandizzi D, Guglielmotti MB, Cabrini RL.

ABSTRACT

BACKGROUND:

Titanium is the most widely used metal in dental implantology. The release of particles from metal structures into the biologic milieu may be the result of electrochemical processes (corrosion) and/or mechanical disruption during insertion, abutment connection, or removal of failing implants. The aim of the present study is to evaluate tissue response of human oral mucosa adjacent to titanium cover screws.

METHODS:

One hundred fifty-three biopsies of the supra-implant oral mucosa adjacent to the cover screw of submerged dental implants were analyzed. Histologic studies were performed to analyze epithelial and connective tissue as well as the presence of metal particles, which were identified using microchemical analysis. Langerhans cells, macrophages, and T lymphocytes were studied using immunohistochemical techniques. The surface of the cover screws was evaluated by scanning electron microscopy (SEM).

RESULTS:

Forty-one percent of mucosa biopsies exhibited metal particles in different layers of the section thickness. Particle number and size varied greatly among specimens. Immunohistochemical study confirmed the presence of macrophages and T lymphocytes associated with the metal particles. Microchemical analysis revealed the presence of titanium in the particles. On SEM analysis, the surface of the screws exhibited depressions and irregularities.

CONCLUSIONS:

The biologic effects seen in the mucosa in contact with the cover screws might be associated with the presence of titanium or other elements, such as aluminum or vanadium. The potential long-term biologic effects of particles on soft tissues adjacent to metallic devices should be further investigated because these effects might affect the clinical outcome of the implant.

J PERIODONTOL. 2013 JAN;84(1):78-83. DOI: 10.1902/JOP.2012.110757. EPUB 2012 MAR 13.

Exfoliative cytology and titanium dental implants: a pilot study.

Olmedo DG, Nalli G, Verdú S, Paparella ML, Cabrini RL.

ABSTRACT

BACKGROUND:

Oral exfoliative cytology is a diagnostic method that involves the study of cells exfoliated from the oral mucosa. Ions/particles released from metallic implants can remain in the peri-implant milieu. The aim of the present study is to assess the presence of metal particles in cells exfoliated from peri-implant oral mucosa around titanium dental implants.

METHODS:

The study comprised 30 patients carrying titanium dental implants, who had neither a metallic prosthesis nor metal restorations in neighboring teeth. Individuals undergoing orthodontic therapy and those who had oral piercing were also excluded from the study. The study sample included patients with and without peri-implantitis. Cytologic samples of the peri-implant area were collected. Samples of the marginal gingiva on the contralateral side of the implant were taken from the same individuals to serve as control. Cytologic analysis was performed using light microscopy. Titanium concentration was determined using inductively coupled plasma-mass spectrophotometry.

RESULTS:

Metal-like particles were observed inside and outside epithelial cells and macrophages in cytologic smears of peri-implant mucosa of both patients with and without peri-implantitis. No particles were found in the control cytologic samples. The concentration of titanium was higher in the peri-implantitis group compared with the group without peri-implantitis; no traces of titanium were observed in controls.

CONCLUSIONS:

Regardless of an inflammatory response, ions/particles are released from the surface of the implant into the biologic milieu. Exfoliative cytology is a simple technique that may be used to detect metal particles in cells exfoliated from the peri-implant mucosa.

BIOMED RES INT. 2013; 2013:539834. DOI: 10.1155/2013/539834. EPUB 2013 SEP 11.

Allergy or tolerance: reduced inflammatory cytokine response and concomitant IL-10 production of lymphocytes and monocytes in symptom-free titanium dental implant patients.

Thomas P, Iglhaut G, Wollenberg A, Cadosch D, Summer B.

ABSTRACT

Hypersensitivity reactions to titanium (Ti) are very rare. Thus, we assessed the proinflammatory response and also potential tolerance favoring in vitro reactivity of human blood lymphocytes and monocytes (PBMC) to Ti in healthy individuals (14 without, 6 with complication-free dental Ti implants). The proliferation index (SI) in lymphocyte transformation test (LTT) and production of cytokines linked to innate immune response (IL-1 β , IL-6, and TNF α) or immune regulation (IL-10) were assessed in response to TiO2 particles or Ti discs. In both groups, the Ti-LTT reactivity was not enhanced (e.g., SI < 3). The control antigen tetanus toxoid (TT) gave adequate reactivity (median SI individuals without/with implant: 20.6 ± 5.97/19.58 ± 2.99). Individuals without implant showed higher cytokine response to Ti materials than individuals with symptom-free implants; for example, TiO2 rutile particle induced increase of IL-1 β 70.27-fold/8.49-fold versus control medium culture. PBMC of 5 of the 6 individuals with complication-free Ti implants showed an ex vivo ongoing production of IL-10 (mean 4.18 ± 2.98 pg/mL)-but none of the 14 controls showed such IL-10 production. Thus in vitro IL-1 β -, IL-6-, and TNF-α production reflects "normal" unspecific immune response to Ti. This might be reduced by production of tolerogenic IL-10 in individuals with symptom-free Ti dental implants.

J PERIODONTOL. 2014 SEP;85(9):1275-82. DOI: 10.1902/JOP.2014.130595. EPUB 2014 JAN 20.

Attachment of Porphyromonas gingivalis to corroded commercially pure titanium and titanium-aluminum-vanadium alloy.

Barão VA, Yoon CJ, Mathew MT, Yuan JC, Wu CD, Sukotjo C.

ABSTRACT

BACKGROUND:
Titanium dental material can become corroded because of electrochemical interaction in the oral environment. The corrosion process may result in surface modification. It was hypothesized that a titanium surface modified by corrosion may enhance the attachment of periodontal pathogens. This study evaluates the effects of corroded titanium surfaces on the attachment of Porphyromonas gingivalis.

METHODS:
Commercially pure titanium (cp-Ti) and titanium-aluminum-vanadium alloy (Ti-6Al-4V) disks were used. Disks were anodically polarized in a standard three-electrode setting in a simulated oral environment with artificial saliva at pH levels of 3.0, 6.5, or 9.0. Non-corroded disks were used as controls. Surface roughness was measured before and after corrosion. Disks were inoculated with P. gingivalis and incubated anaerobically at 37 °C. After 6 hours, the disks with attached P. gingivalis were stained with crystal violet, and attachment was expressed based on dye absorption at optical density of 550 nm. All assays were performed independently three times in triplicate. Data were analyzed by two-way analysis of variance, the Tukey honestly significant difference test, t test, and Pearson's correlation test ($\alpha = 0.05$).

RESULTS:
Both cp-Ti and Ti-6Al-4V alloy-corroded disks promoted significantly more bacterial attachment (11.02 % and 41.78 %, respectively; $P < 0.0001$) than did the non-corroded controls. Significantly more (11.8 %) P. gingivalis attached to the cp-Ti disks than to the Ti-6Al-4V alloy disks ($P < 0.05$). No significant difference in P. gingivalis attachment was noted among the corroded groups for both cp-Ti and Ti-6Al-4V alloy ($P > 0.05$). There was no significant correlation between surface roughness and P. gingivalis attachment.

CONCLUSION:
A higher degree of corrosion on the titanium surface may promote increased bacterial attachment by oral pathogens.

J BIOMED MATER RES A. 2014 MAY;102(5):1439-48. DOI: 10.1002/JBM.A.34822. EPUB 2013 JUN 21.

Impact through time of different sized titanium dioxide particles on biochemical and histopathological parameters.

Bruno ME, Tasat DR, Ramos E, Paparella ML, Evelson P, Rebagliati RJ, Cabrini RL, Guglielmotti MB, Olmedo DG.

ABSTRACT

Due to corrosion, a titanium implant surface can be a potential source for the release of micro (MPs) and nano-sized particles (NPs) into the biological environment. This work sought to evaluate the biokinetics of different sized titanium dioxide particles (TiO2) and their potential to cause cell damage. Wistar rats were intraperitoneally injected with 150 nm, 10 nm, or 5nm TiO2 particles. The presence of TiO2 particles was evaluated in histologic sections of the liver, lung, and kidney and in blood cells at 3 and 12 months. Ultrastructural analysis of liver and lung tissue was performed by TEM, deposit concentration in tissues was determined spectroscopically, and oxidative metabolism was assessed by determining oxidative membrane damage, generation of superoxide anion (O2(-)), and enzymatic and non-enzymatic antioxidants. TiO2 particles were observed inside mononuclear blood cells and in organ parenchyma at 3 and 12 months. TiO2 deposits were consistently larger in liver than in lung tissue. Alveolar macrophage O2(-) generation and average particle size correlated negatively ($p < 0.05$). NPs were more reactive and biopersistent in lung tissue than MPs. Antioxidant activity, particularly in the case of 5 nm particles, failed to compensate for membrane damage in liver cells; the damage was consistent with histological evidence of necrosis.

TOXICOL REP. 2015 FEB 19;2:765-774. DOI: 10.1016/J.TOXREP.2015.02.004. ECOLLECTION 2015.

Comparative study of the cytotoxic and genotoxic potentials of zinc oxide and titanium dioxide nanoparticles.

Khan M, Naqvi AH, Ahmad M.

ABSTRACT

Nanoparticles (NPs) of zinc oxide (ZnO) and titanium dioxide (TiO2) are receiving increasing attention due to their widespread applications. The aim of this study was to evaluate the toxic effect of ZnO and TiO2 NPs at different concentrations (50, 100, 250 and 500 ppm) and compare them with their respective salts using a battery of cytotoxicity, and genotoxicity parameters. To evaluate cytotoxicity, we have used human erythrocytes and for genotoxic studies human lymphocytes have been used as in vitro model species. Concentration dependent hemolytic activity to RBC's was obtained for both NPs. ZnO and TiO2 NPs resulted in 65.2 % and 52.5 % hemolysis at 250 ppm respectively indicating that both are cytotoxic to human RBCs. Antioxidant enzymes assays were also carried out in their respective hemolysates. Both nanoparticles were found to generate reactive oxygen species (ROS) concomitant with depletion of glutathione and GST levels and increased SOD, CAT and lipid peroxidation in dose dependent manner. ZnO and TiO2 NPs exerted roughly equal oxidative stress in terms of aforementioned stress markers. Genotoxic potential of both the NPs was investigated by in vitro alkaline comet assay. DNA damage induced by the NPs was concentration dependent and was significantly greater than their ionic forms at 250 and 500 ppm concentrations. Moreover, the nanoparticles of ZnO were significantly more genotoxic than those of TiO2 at higher concentrations. The toxicity of these NPs is due to the generation of ROS thereby causing oxidative stress.

CLIN IMPLANT DENT RELAT RES. 2015 AUG;17(4):681-92. DOI: 10.1111/CID.12167. EPUB 2013 NOV 28.

Surface Damage on Dental Implants with Release of Loose Particles after Insertion into Bone.

Senna P, Antoninha Del Bel Cury A, Kates S, Meirelles L.

ABSTRACT

BACKGROUND:
Modern dental implants present surface features of distinct dimensions that can be damaged during the insertion procedure into bone.

PURPOSE:
The aims of this study were (1) to quantify by means of roughness parameters the surface damage caused by the insertion procedure of dental implants and (2) to investigate the presence of loose particles at the interface.

MATERIALS AND METHODS:
Three groups of dental implants representing different surface topographies were inserted in fresh cow rib bone blocks. The surface roughness was characterized by interferometry on the same area before and after the insertion. Scanning electron microscopy (SEM)-back-scattered electron detector (BSD) analysis was used to identify loose particles at the interface.

RESULTS:
The amplitude and hybrid roughness parameters of all three groups were lower after insertion. The surface presenting predominance of peaks (Ssk [skewness] > 0) associated to higher structures (height parameters) presented higher damage associated to more pronounced reduction of material volume. SEM-BSD images revealed loose titanium and aluminum particles at the interface mainly at the crestal cortical bone level.

CONCLUSIONS:
Shearing forces during the insertion procedure alters the surface of dental implants. Loose metal particles can be generated at bone-implant interface especially around surfaces composed mainly by peaks and with increased height parameters.

J MED MICROBIOL. 2016 JUL;65(7):596-604.
DOI: 10.1099/JMM.0.000267. EPUB 2016 APR 19.

Bacterial adhesion and biofilm formation on yttria-stabilized, tetragonal zirconia and titanium oral implant materials with low surface roughness - an in situ study.

Al-Ahmad A, Karygianni L, Schulze Wartenhorst M, Bächle M, Hellwig E, Follo M, Vach K, Han JS.

ABSTRACT

Bacterially-driven mucosal inflammation and the development of periimplantitis can lead to oral implant failure. In this study, initial bacterial adhesion after 2 h, and biofilm formation after 1 day and 3 days, were analysed in situ on novel 3 mol% yttria-stabilized tetragonal zirconia polycrystal samples, as well as on alumina and niobium co-doped yttria-stabilized tetragonal zirconia samples. Pure titanium implant material and bovine enamel slabs served as controls. The initially adherent oral bacteria were determined by 4′,6-diamidino-2-phenylindole-staining. Biofilm thickness, surface covering grade and content of oral streptococci within the biofilm were measured by fluorescence in situ hybridization. No significant differences between the ceramic and titanium surfaces were detectable for either initial bacterial adhesion or the oral streptococci content of the in situ biofilm. The oral biofilm thickness on the implant surfaces were almost doubled after three days compared to the first day of oral exposure. Nevertheless, the biofilm thickness values among the different implant surfaces and controls did not differ significantly for any time point of measurement after 1 day or 3 days of biofilm formation. Significant differences in the covering grade were only detected between day 1 and day 3 for each tested implant material group. The content of oral streptococci increased significantly in parallel with the increase in biofilm age from day 1 to day 3. In conclusion, oral implant zirconia surfaces with low surface roughness are comparable to titanium surfaces with respect to initial bacterial adhesion and biofilm formation.

INT J MOL SCI. 2018 APR 6;19(4). PII: E1101.
DOI: 10.3390/IJMS19041101.

Novel Nanoparticulate and Ionic Titanium Antigens for Hypersensitivity Testing.

Høl PJ, Kristoffersen EK, Gjerdet NR, Pellowe AS.

ABSTRACT

Titanium is used in a wide variety of materials ranging from medical devices to materials used in everyday life. Adverse biological reactions that could occur in patients, consumers, and workers should be monitored and prevented. There is a lack of available agents to test and predict titanium-related hypersensitivity. The aim of this study was to develop two bioavailable titanium substances in ionic and nanoparticulate form to serve as antigens for hypersensitivity testing in vitro. Peripheral blood mononuclear cells from 20 test subjects were stimulated with the antigens and secretion of monocytic and lymphatic cytokines and chemokines were measured by a multiplex bead assay. Lymphocyte stimulation indices were also determined in a subset of test subjects by measuring CD69 and HLA-DR expression by flow cytometry. Cytokine profiling revealed that both antigens increased production of typical monocyte and macrophage secreted cytokines after 24 h, with significant increases in IL-1β IL-7, IL-10, IL-12, IL-2R, IL-6, GM-CSF, TNF-β , IL-1RA, MIP-1β , MIP-1β , IFN-β , and IL-15. Lymphatic cytokines and chemokines were not significantly induced by activation. After seven days of stimulation, ionic-Ti (2.5 β g/mL) caused proliferation (stimulation index > 2) of CD4+ cells and CD8+ cells in all persons tested (N = 6), while titanium dioxide nanoparticles (50 β g/mL) only caused significant proliferation of CD4+ cells. Our preliminary results show that the experimental titanium antigens, especially the ionic form, induce a general inflammatory response in vitro. A relevant cohort of test subjects is required to further elucidate their potential for predictive hypersensitivity testing.

1. TITANIUM IMPLANTOLOGY AND PERIIMPLANTITIS

2.2 Clinically relevant Studies and Papers

J BONE JOINT SURG AM. 2000
APR;82(4):457-76.

Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement.

Urban RM, Jacobs JJ, Tomlinson MJ, Gavrilovic J, Black J, Peoc'h M.

ABSTRACT

BACKGROUND:
The importance of particles generated by wear and corrosion of joint replacement prostheses has been understood primarily in the context of the local effects of particle-induced periprosthetic osteolysis and aseptic loosening. We studied dissemination of wear particles in patients with total hip and knee replacement to determine the prevalence of and the histopathological response to prosthetic wear debris in the liver, spleen, and abdominal paraaortic lymph nodes.

METHODS:
Postmortem specimens from twenty-nine patients and biopsy specimens from two living patients with a failed replacement were analyzed. Specimens of tissue obtained from the cadavera of fifteen patients who had not had a joint replacement served as controls. The concentration of particles and the associated tissue response were characterized with the use of light microscopy of stained histological sections. Metallic particles were identified by electron microprobe analysis. Polyethylene particles were studied with the use of oil-red-O stain and polarized light microscopy. The composition of polyethylene particles was confirmed in selected cases by Fourier transform infrared spectroscopy and hot-stage thermal analysis. Twenty-one of the patients studied post mortem had had a primary total joint replacement. Eleven of them had had a hip prosthesis for a mean of sixty-nine months (range, forty-three to 171 months), and ten had had a knee replacement for a mean of eighty-four months (range, thirty-one to 179 months). The other eight patients studied post mortem had had a hip replacement in which one or more components had loosened and had been revised. The mean time between the initial arthroplasty and the time of death was 174 months (range, forty-seven to 292 months), and the mean time between the last revision procedure and the time of death was seventy-one months (range, one to 130 months).

RESULTS:
Metallic wear particles in the liver or spleen were more prevalent in patients who had had a failed hip arthroplasty (seven of eight) than in patients who had had a primary hip (two of eleven) or knee replacement (two of ten). The principal source of wear particles in the majority of these patients involved secondary nonbearing surfaces rather than wear between the two primary bearing surfaces as intended. In one living patient, dissemination of titanium alloy particles from a hip prosthesis with mechanical failure was associated with a visceral granulomatous reaction and hepatosplenomegaly, which required operative and medical treatment. Metallic wear particles were detected in the paraaortic lymph nodes in 68 percent (nineteen) of the twenty-eight patients with an implant from whom lymph nodes were available for study. In 38 percent (eleven) of all twenty-nine patients with an implant who were studied post mortem, metallic particles had been further disseminated to the liver or spleen, where they were usually found within small aggregates of macrophages occurring as infiltrates without apparent pathological importance. Polyethylene particles elicited a similar response. They were identified in the paraaortic lymph nodes of 68 percent (nineteen) of the twenty-eight patients and the liver or spleen of 14 percent (four) of the twenty-nine patients. The majority of the disseminated wear particles were less than one micrometer in size. Currently available methods lack the sensitivity and specificity necessary to detect very low concentrations of submicrometer polyethylene particles and probably underestimated the prevalence of polyethylene wear debris in the liver and spleen.

CONCLUSIONS:
In this study, systemic distribution of metallic and polyethylene wear particles was a common finding, both in patients with a previously failed implant and in those with a primary total joint prosthesis. The prevalence of particles in the liver or spleen was greater after reconstructions with mechanical failure. (ABSTRACT TRUNCATED)

CLIN IMPLANT DENT RELAT RES. 2007 JUN;9(2):112-5.

Breast metastasis around dental implants: a case report.

Dib LL, Soares AL, Sandoval RL, Nannmark U.

ABSTRACT

BACKGROUND:
Metastases to the oral cavity and to the jaws are rare; hence, the clinical manifestations of the oral metastasis lesion could frequently be simulating general pathologic entities, making the diagnosis a challenging process to the dental team. Local factors, such as trauma, have been observed to facilitate the growth of blood-borne tumors. To this end, surgical procedures such as fixture placement might cause cancer cells to spread.

PURPOSE:
Careful clinical examination is a valuable help in diagnosing oral lesions, which can improve the quality of life of patients and reduce the risks of oral complications.

MATERIALS AND METHODS:
A female patient was referred to the clinic with symptoms of irritation, swelling, and pain associated with implants in the mandible and the maxilla.

RESULTS:
Clinical examination, x-ray, and histopathology revealed that the patients suffered from a metastatic lesion, primary tumor being an adenocarcinoma of the breast diagnosed at the same time.

CONCLUSION:
Optimal clinical examination in conjunction with radiography and histopathology is a necessity in order to discover malignant lesions in time. Routine dental check-ups must comprise more thorough soft-tissue examination.

CLIN ORAL IMPLANTS RES. 2007 AUG;18(4):540-3. EPUB 2007 APR 30.

Plasmacytoma of the mandible associated with a dental implant failure: a clinical report.

Poggio CE.

ABSTRACT

The case report of a patient is presented who had been suffering from a plasmacytoma of the spine several years back, and who had developed a new plasmacytoma of the mandible, 3 years subsequent to the insertion of a dental implant. This second solitary lesion occurred 15 years after the first one, and without signs of conversion to multiple myeloma. Research in animal models has shown multinucleated giant cells, belonging to the monocyte-macrophage lineage, persisting between the titanium surface and the lymphohemopoietic compartment, at least 1.5 years after implant insertion. Factors that increase the proliferative activity of precursor B cells, for example a protracted macrophage activation, are likely to increase the risk of B cell oncogenesis. A possible role of the titanium surface in an increase of precursor B cell proliferative activity, thus facilitating a new localization, was evaluated.

INT J PROSTHODONT. 2007
JAN-FEB;20(1):51-4.

An unusual case of implant f ailure.

Verhoeven JW, Cune MS, van Es RJ.

ABSTRACT
A 67-year-old woman was referred with a rapidly progressing swelling in the left canine region of the edentulous mandible. Nine months earlier, 2 permucosal implants had been placed in her atrophic anterior mandible. A few weeks after implant placement, an inoperable carcinoma of the lung had been diagnosed. This tumor was treated with a combination of chemotherapy and radiotherapy. After 3 months, the implants were provided with a Dolder bar supporting an overdenture. Subsequently, progressive inflammation developed around the left implant and removal of the implant was necessary. When progressive swelling of the mucosa developed at the previous implant site, the patient was referred to an oral and maxillofacial surgeon. The swelling measured 35 mm in diameter and was biopsied. It was diagnosed as a metastasis of the lung carcinoma to the mandible. The tumor of the jaw was treated with local radiotherapy.

J AM DENT ASSOC. 2008 AUG;139(8):1061-5.

Oral squamous cell carcinoma associated with symphyseal dental implants: an unusual case report.

Gallego L, Junquera L, Baladrón J, Villarreal P.

ABSTRACT
BACKGROUND:
The development of squamous cell carcinoma (SCCa) around dental implants is an uncommon pathological manifestation. This case report describes a patient with history of oral lichen planus (OLP) and previous SCCa of the gingiva who developed SCCa adjacent to symphyseal implants.

CASE DESCRIPTION:
An 81-year-old edentulous woman with history of OLP developed an in situ SCCa on the left mandibular edentulous ridge. One of the authors, an oral and maxillofacial surgeon, performed a marginal mandibular resection of the lesion. Functional oral rehabilitation was achieved by means of two endosseous symphyseal implants. Three years after the patient underwent implant-supported reconstruction, the oral and maxillofacial surgeon detected an exophytic mass adjacent to the right implant and diagnosed it as recurrent SCCa. Two of the authors performed a marginal mandibular resection. One year later, the patient developed a recurrence over the resected area, requiring segmental mandibulectomy.

CLINICAL IMPLICATIONS:
This case report demonstrates that recurrent primary malignancy can masquerade as benign peri-implant complications. A high degree of vigilance is required in the follow-up of patients with previous cancer or premalignant lesions.

J AM DENT ASSOC. 2008 AUG;139(8):1052-9.

Maxillary osteosarcoma associated with a dental implant: report of a case and review of the literature regarding implant-related sarcomas.

McGuff HS, Heim-Hall J, Holsinger FC, Jones AA, O'Dell DS, Hafemeister AC.

ABSTRACT

BACKGROUND:

The development of malignant neoplasms has been reported as a rare complication of the use of implanted biomaterials. The majority of these cases have been sarcomas related to orthopedic hardware. The authors present the first reported case of a sarcoma arising in association with a dental implant.

CASE DESCRIPTION:

A 38-year-old woman developed a low-grade chondroblastic osteosarcoma of the right maxilla 11 months after receiving a titanium dental implant. She was treated with systemic chemotherapy and then a maxillary resection. As of this publication, 47 months later, she is alive and disease-free.

CLINICAL IMPLICATIONS:

The use of endosseous implants has been associated with a low risk for the development of cancer. As the use of dental implants continues to expand, dentists need to be aware of this rare but devastating complication.

CLIN ORAL IMPLANTS RES. 2008 AUG;19(8):823-35. DOI: 10.1111/J.1600-0501.2008.01544.X.

Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients.

Sicilia A, Cuesta S, Coma G, Arregui I, Guisasola C, Ruiz E, Maestro A.

ABSTRACT

BACKGROUND:

In dentistry, allergic reactions to Ti implants have not been studied, nor considered by professionals. Placing permanent metal dental implants in allergic patients can provoke type IV or I reactions. Several symptoms have been described, from skin rashes and implant failure, to non-specific immune suppression.

OBJECTIVE:

Our objective was to evaluate the presence of titanium allergy by the anamnesis and examination of patients, together with the selective use of cutaneous and epicutaneous testing, in patients treated with or intending to receive dental implants of such material.

MATERIAL AND METHODS:

Thirty-five subjects out of 1500 implant patients treated and/or examined (2002-2004) were selected for Ti allergy analysis. Sixteen presented allergic symptoms after implant placement or unexplained implant failures [allergy compatible response group (ACRG)], while 19 had a history of other allergies, or were heavily Ti exposed during implant surgeries or had explained implant failures [predisposing factors group (PFG)]. Thirty-five controls were randomly selected (CG) in the Allergy Centre. Cutaneous and epicutaneous tests were carried out.

RESULTS:

Nine out of the 1500 patients displayed positive (+) reactions to Ti allergy tests (0.6 %): eight in the ACRG (50 %), one in the PFG (5.3 %)(P=0.009) and zero in the control group. Five positives were unexplained implant failures (five out of eight).

CONCLUSIONS:

Ti allergy can be detected in dental implant patients, even though its estimated prevalence is low (0.6 %). A significantly higher risk of positive allergic reaction was found in patients showing post-op allergy compatible response (ACRG), in which cases allergy tests could be recommended.

INT J ORAL MAXILLOFAC SURG. 2010 MAY;39(5):503-7. DOI: 10.1016/J.IJOM.2009.11.007. EPUB 2009 DEC 11.

Reactive lesions of peri-implant mucosa associated with titanium dental implants: a report of 2 cases.

Olmedo DG, Paparella ML, Brandizzi D, Cabrini RL.

ABSTRACT

The aim of this study was to report 2 novel clinical cases of reactive lesions of the peri-implant mucosa associated with titanium dental implants where metal-like particles were observed histologically. In both cases, the lesions were diagnosed as epulis, based on clinical evidence. Extirpation biopsies were carried out. Case 1 was diagnosed as pyogenic granuloma and case 2 as peripheral giant cell granuloma. The presence of metal-like particles in the tissues suggests that the etiology of the lesions might be related to the corrosion process of the metal structure. This is the first case of pyogenic granuloma to be reported in association with dental implants. All clinical cases of soft tissue lesions associated with implants should be reported to contribute to the understanding of the etiology and pathogeny of these lesions.

CLIN COSMET INVESTIG DENT. 2013; 5: 57–61. PUBLISHED ONLINE 2013 AUG 19. DOI: 10.2147/CCIDE.S35170.

Allergy related to dental implant and its clinical significance.

Chaturvedi TP.

ABSTRACT

The oral cavity provides an ideal and unique environment for study of biological processes involving metallic dental aids. Dental materials within the mouth interact continually with physiological fluids. Oral tissues are exposed to a veritable bombardment of both chemical and physical stimuli as well as the metabolism of many species of bacteria; yet, for the most part, oral tissues remain healthy. The pH of saliva varies from 5.2 to 7.8. Teeth, restorations, or any prosthesis including dental implants in the oral cavity have to function in one of the most inhospitable environments in the human body. They are subject to larger temperature and pH variations than most other parts of the body. Corrosion, the graded degradation of materials by electrochemical attack, is of concern particularly when dental implants are placed in the hostile electrolytic environment provided by the human mouth. Allergic reactions may occur from the presence of ions produced from the corrosion of implants. The present article describes various manifestations of allergic reactions due to implant material in the oral cavity.

BIOMED RES INT. 2015; 2015:137287. DOI: 10.1155/2015/137287. EPUB 2015 MAR 25.

Biomaterial hypersensitivity: is it real? Supportive evidence and approach considerations for metal allergic patients following total knee arthroplasty.

Mitchelson AJ, Wilson CJ, Mihalko WM, Grupp TM, Manning BT, Dennis DA, Goodman SB, Tzeng TH, Vasdev S, Saleh KJ.

ABSTRACT

The prospect of biomaterial hypersensitivity developing in response to joint implant materials was first presented more than 30 years ago. Many studies have established probable causation between first-generation metal-on-metal hip implants and hypersensitivity reactions. In a limited patient population, implant failure may ultimately be related to metal hypersensitivity. The examination of hypersensitivity reactions in current-generation metal-on-metal knee implants is comparatively limited. The purpose of this study is to summarize all available literature regarding biomaterial hypersensitivity after total knee arthroplasty, elucidate overall trends about this topic in the current literature, and provide a foundation for clinical approach considerations when biomaterial hypersensitivity is suspected.

HAUTARZT. 2016 MAY;67(5):373-9. DOI: 10.1007/S00105-016-3790-6.

Metal implant sensitivity: clinical and histological presentation.

Hartmann D, Letulé V, Schneider JJ, Flaig MJ.

ABSTRACT

Metal implant sensitivity (intolerance) can cause pain, reduced mobility, loosening of the implant and skin rashes. Knowledge of differential diagnoses, histology and appropriate diagnostics are essential for proper diagnosis. To outline typical clinical signs and histology in metal-implant-associated skin lesions we present three exemplary patients from our implant allergy outpatient department and give an overview of the current literature regarding metal implant sensitivity. In patients with a negative patch test the lymphocyte transformation test may reveal metal sensitization. Even "pure" titanium alloys may contain traces of nickel. The histology of implant-associated skin reactions goes from teleangiectatic post-implantation erythema to eczema and vasculitis. Based on the synopsis of history, clinical picture, allergological testing and histology, metal implant sensitivity can be diagnosed more precisely.

J PROSTHODONT RES. 2016 JUL;60(3):213-9. DOI: 10.1016/J.JPOR.2015.12.004. EPUB 2016 JAN 8.

Allergic contact dermatitis caused by titanium screws and dental implants.

Hosoki M, Nishigawa K, Miyamoto Y, Ohe G, Matsuka Y.

ABSTRACT

PATIENTS:

Titanium has been considered to be a non-allergenic material. However, several studies have reported cases of metal allergy caused by titanium-containing materials. We describe a 69-year-old male for whom significant pathologic findings around dental implants had never been observed. He exhibited allergic symptoms (eczema) after orthopedic surgery. The titanium screws used in the orthopedic surgery that he underwent were removed 1 year later, but the eczema remained. After removal of dental implants, the eczema disappeared completely.

DISCUSSION:

Titanium is used not only for medical applications such as plastic surgery and/or dental implants, but also for paints, white pigments, photocatalysts, and various types of everyday goods. Most of the usage of titanium is in the form of titanium dioxide. This rapid expansion of titanium-containing products has increased percutaneous and permucosal exposure of titanium to the population.

CONCLUSIONS:

In general, allergic risk of titanium material is smaller than that of other metal materials. However, we suggest that pre-implant patients should be asked about a history of hypersensitivity reactions to metals, and patch testing should be recommended to patients who have experienced such reactions.

ORTHOPEDICS. 2016 MAY;39(3 SUPPL):S24-30. DOI: 10.3928/01477447-20160509-08.

Influence of Surface Coating on Metal Ion Release: Evaluation in Patients With Metal Allergy.

Thomas P, Weik T, Roider G, Summer B, Thomsen M.

ABSTRACT

Nickel, chromium, and cobalt in stainless steel and Cobalt-chrome-molybdenum (CoCrMo) alloys may induce allergy. The objectives of this study were to evaluate surface coating regarding ion release, patch test reactivity, and arthroplasty performance. Materials and methods included patch test in 31 patients with metal allergy and 30 patients with no allergy to stainless steel and CoCrMo disks that are uncoated or coated by titanium nitride/zirconium nitride (TiN/ZrN). Assessment include atomic absorption spectrometry of released nickel, cobalt, and chromium from the disks after exposure to distilled water, artificial sweat and culture medium. Results showed that both coatings reduced the nickel and chromium release from stainless steel and CoCrMo disks and mostly the cobalt release from the disks (maximally 11.755 µg/cm(2)/5 d to 1.624 by Ti-N and to 0.442 by ZrN). Six of the 31 patients with metal allergy reacted to uncoated disks, but none reacted to the coated disks. The current authors report on exemplary patients with metal allergy who had symptom relief by revision with surface-coated arthroplasty. The authors concluded that the surface coating may prevent cutaneous and peri-implant allergic reactions. [Orthopedics. 2016; 39(3):S24-S30.].

J INDIAN SOC PERIODONTOL. 2017 MAY-JUN;21(3):192-194. DOI: 10.4103/JISP.JISP_184_16.

Titanium particles in tissues from peri-implant mucositis: An exfoliative cytology-based pilot study.

Penmetsa SLD, Shah R, Thomas R, Kumar ABT, Gayatri PSD, Mehta DS.

ABSTRACT

BACKGROUND:
To evaluate the presence of titanium particles in the peri-implant mucosa of unloaded single implants.

MATERIALS AND METHODS:
Forty participants with single unloaded implants were selected. They were divided equally into two groups: Group 1 with mild and Group 2 with moderate-to-severe peri-implant mucositis. Cytologic smears of peri-implant mucosa were obtained using cytobrush during second-stage surgery.

RESULTS:
Study states that 60 % of participants of Group 2 were positive for titanium particles in peri-implant cytology.

CONCLUSION:
This study concludes that the titanium particles might be the initiators of the inflammation around implant.

J PERIODONTOL. 2017 MAY;88(5):436-442. DOI: 10.1902/JOP.2016.160524. EPUB 2016 NOV 18.

Increased Levels of Dissolved Titanium are Associated With Peri-Implantitis - A Cross-Sectional Study.

Safioti LM, Kotsakis GA, Pozhitkov AE, Chung WO, Daubert DM.

ABSTRACT

BACKGROUND:
Peri-implantitis represents a disruption of the biocompatible interface between the titanium dioxide layer of the implant surface and the peri-implant tissues. Increasing preclinical data suggest that peri-implantitis microbiota not only triggers an inflammatory immune response but also causes electrochemical alterations of the titanium surfaces, i.e., corrosion, that aggravate this inflammatory response. Thus, it was hypothesized that there is an association between dissolution of titanium from dental implants, which suggests corrosion, and peri-implantitis in humans. The objective of this study is to compare levels of dissolved titanium in submucosal plaque collected from healthy implants and implants with peri-implantitis.

METHODS:
Submucosal plaque from 20 implants with peri-implantitis and 20 healthy implants was collected with sterile curets from 30 participants. Levels of titanium were quantified using inductively coupled plasma mass spectrometry and normalized for mass of bacterial DNA per sample to exclude confounding by varying amounts of plaque per site. Statistical analysis was performed using generalized estimated equations to adjust for clustering of implants per participant.

RESULTS:
Implants with peri-implantitis harbored significantly higher mean levels of titanium (0.85 ± 2.47) versus healthy implants (0.07 ± 0.19) after adjusting for amount of plaque collected per site (P = 0.033).

CONCLUSIONS:
Greater levels of dissolved titanium were detected in submucosal plaque around implants with peri-implantitis compared with healthy implants, indicating an association between titanium dissolution and peri-implantitis. Factors triggering titanium dissolution, as well as the role of titanium corrosion in the peri-implant inflammatory process, warrant further investigation.

CLIN IMPLANT DENT RELAT RES. 2018 DEC;20(6):945-953. DOI: 10.1111/CID.12676. EPUB 2018 SEP 25.

Titanium as a modifier of the peri-implant microbiome structure.

Daubert D, Pozhitkov A, McLean J, Kotsakis G.

ABSTRACT

BACKGROUND:
Recent data support the implication of accelerated titanium dissolution products in peri-implantitis. It is unknown whether these dissolution products have an effect on the peri-implant microbiome, the target of existing peri-implantitis therapies.

PURPOSE:
This study assessed the relationship between the peri-implant microbiome, dissolved titanium levels, and peri-implantitis.

MATERIALS AND METHODS:
Clinical, microbiome, and titanium data were collected from a periodontal population having implants in function for 10 years. Clinical examinations were performed, and submucosal plaque samples were collected from the deepest site per implant. An aliquot of the sample was used for 16S rRNA gene sequencing, with the remainder analyzed for titanium quantity using mass spectrometry. Sequences were clustered into taxonomic units at 97 % minimum sequence similarity using the QIIME pipeline approach.

RESULTS:
Fifteen implants were assessed. According to established case definitions, six had a diagnosis of peri-implantitis; nine were healthy. The genera Streptococcus, Prevotella and Haemophilus characterized peri-implant health. Peri-implantitis was associated with a marked increase in Veillonella. Quantities of dissolved titanium were identified in 40% of sites. Titanium presence was associated with peri-implant disease status (P = .02) and correlated to the first principal component of the microbiome (rho = 0.552) and its alpha-diversity (rho = -0.496). Canonical correlation analyses found that titanium levels, but not health or disease status of the implant, were significantly associated with the microbiota composition (P = .045).

CONCLUSIONS:
These findings suggest an association between titanium dissolution products and peri-implantitis and support a role for these products in modifying the peri-implant microbiome structure and diversity.

J PROSTHODONT RES. 2018 OCT;62(4):426-431. DOI: 10.1016/J.JPOR.2018.03.003. EPUB 2018 APR 16.

Cross-sectional observational study exploring clinical risk of titanium allergy caused by dental implants.

Hosoki M, Nishigawa K, Tajima T, Ueda M, Matsuka Y.

ABSTRACT

PURPOSE:
Studies have reported cases of metal allergy caused by titanium-containing materials. We wished to clarify the relationship between titanium allergy and dental implants by describing patients who suffered allergic symptoms after they had received such implants.

METHODS:
A total of 270 patients who visited a Dental Metal Allergy Clinic at Tokushima University Hospital from April 2010 to March 2014 were the study cohort. Patch testing with 28 types of metal allergens (including four titanium allergens) was undertaken for patients.

RESULTS:
A total of 217 patients (80.4 %) exhibited allergy-positive reactions to at least one type of metal allergen. Mercury, palladium, chromium and nickel exhibited a higher prevalence of allergy-positive reactions than other metals. Sixteen patients visited our clinic suffering allergic symptoms after receiving dental implants. Eleven of those patients exhibited allergy-positive reactions for any of the metal allergens, and 4 of these patients had allergy-positive reactions against titanium allergens. The total number of allergy-positive reactions for titanium allergens among all 270 patients was 17 (6.3 %). No patient exhibited a positive reaction only for the titanium allergen.

CONCLUSIONS:
The prevalence of allergy-positive reactions for titanium allergens was lower than for other metal allergens. We suggest examination of pre-implant patients who have a history of hypersensitivity reactions to metals.

EPMA J. 2018 JUN 8;9(3):331-343. DOI: 10.1007/S13167-018-0138-6. ECOLLECTION 2018 SEP.

Titanium implants and silent inflammation in jawbone-a critical interplay of dissolved titanium particles and cytokines TNF-α and RANTES/CCL5 on overall health?

Lechner J, Noumbissi S, von Baehr V.

ABSTRACT

BACKGROUND AND INTRODUCTION:
It is a well-known fact that titanium particles deriving from dental titanium implants (DTI) dissolve into the surrounding bone. Although titanium (TI) is regarded as a compatible implant material, increasing concern is coming up that the dissolved titanium particles induce inflammatory reactions around the implant. Specifically, the inflammatory cytokine tumor necrosis factor-alpha (TNF-α) is expressed in the adjacent bone. The transition from TNF-α-induced local inflammation following insertion of DTI surgery to a chronic stage of "silent inflammation" could be a neglected cause of unexplained medical conditions.

MATERIAL AND METHODS:
The signaling pathways involved in the induction of cytokine release were analyzed by multiplex analysis. We examined samples of jawbone (JB) for seven cytokines in two groups: specimens from 14 patients were analyzed in areas of DTI for particle-mediated release of cytokines. Each of the adjacent to DTI tissue samples showed clinically fatty degenerated and osteonecrotic medullary changes in the JB (FDOJ). Specimens from 19 patients were of healthy JB. In five cases, we measured the concentration of dissolved Ti particles by spectrometry.

RESULTS:
All DTI-FDOJ samples showed RANTES/CCL5 (R/C) as the only extremely overexpressed cytokine. DTI-FDOJ cohort showed a 30-fold mean overexpression of R/C as compared with a control cohort of 19 healthy JB samples. Concentration of dissolved Ti particles in DTI-FDOJ was 30-fold higher than an estimated maximum of 1.000 µg/kg.

DISCUSSION:
As R/C is discussed in the literature as a possible contributor to inflammatory diseases, the here-presented research examines the question of whether common DTI may provoke the development of chronic inflammation in the jawbone in an impaired state of healing. Such changes in areas of the JB may lead to hyperactivated signaling pathways of TNF-α induced R/C overexpression, and result in unrecognized sources of silent inflammation. This may contribute to disease patterns like rheumatic arthritis, multiple sclerosis, and other systemic-inflammatory diseases, which is widely discussed in scientific papers.

CONCLUSION:
From a systemic perspective, we recommend that more attention be paid to the cytokine cross-talk that is provoked by dissolved Ti particles from DTI in medicine and dentistry. This may contribute to further development of personalized strategies in preventive medicine.

2.3 General Reviews and Overviews

INDIAN J DENT RES. 2009
JAN-MAR;20(1):91-8.

An overview of the corrosion aspect of dental implants (titanium and its alloys).

Chaturvedi TP.

ABSTRACT
Titanium and its alloys are used in dentistry for implants because of its unique combination of chemical, physical, and biological properties. They are used in dentistry in cast and wrought form. The long term presence of corrosion reaction products and ongoing corrosion lead to fractures of the alloy-abutment interface, abutment, or implant body. The combination of stress, corrosion, and bacteria contribute to implant failure. This article highlights a review of the various aspects of corrosion and biocompatibility of dental titanium implants as well as suprastructures. This knowledge will also be helpful in exploring possible research strategies for probing the biological properties of materials.

HINDAWI PUBLISHING CORPORATION
ADVANCES IN TRIBOLOGY. VOLUME 2009,
ARTICLE ID 250986, 12 PAGES
DOI:10.1155/2009/250986.

Significance of Tribocorrosion in Biomedical Applications: Overview and Current Status

Mathew MT, Pai PS, Pourzal R, Fischer A, Wimmer MA.

ABSTRACT
Recently, "tribocorrosion," a research area combining the science of tribology and corrosion, has drawn attention from scientists and engineers belonging to a wide spectrum of research domains. This is due to its practical impact on daily life and also the accompanying economical burdens. It encompasses numerous applications including the offshore, space, and biomedical industry, for instance, in the case of artificial joints (Total Hip Replacement, THR) in orthopedic surgery, where implant metals are constantly exposed to tribological events (joint articulations) in the presence of corrosive solutions, that is, body fluids. Keeping the importance of this upcoming area of research in biomedical applications in mind, it was thought to consolidate the work in this area with some fundamental aspects so that a comprehensive picture of the current state of knowledge can be depicted. Complexity of tribocorrosion processes has been highlighted, as it is influenced by several parameters (mechanical and corrosion) and also due to the lack of an integrated/efficient test system. Finally a review of the recent work in the area of biotribocorrosion is provided, by focusing on orthopedic surgery and dentistry.

ACTA ODONTOL LATINOAM. 2009;22(1):3-9.

The issue of corrosion in dental implants: a review.

Olmedo DG, Tasat DR, Duffó G, Guglielmotti MB, Cabrini RL.

ABSTRACT

Pure titanium or titanium alloys, and to a lesser extent, zirconium, are metals that are often used in direct contact with host tissues. These metallic biomaterials are highly reactive, and on exposure to fluid media or air, quickly develop a layer of titanium dioxide (TiO2) or zirconium dioxide (ZrO2). This layer of dioxide forms a boundary at the interface between the biological medium and the metal structure, determining the degree of biocompatibility and the biological response of the implant. Corrosion is the deterioration a metal undergoes as a result of the surrounding medium (electrochemical attack), which causes the release of ions into the microenvironment. No metal or alloy is entirely inert in vivo. Corrosion phenomena at the interlace are particularly important in the evolution of both dental and orthopedic implants and one of the possible causes of implant failure after initial success. This paper comprises a review of literature and presents results of our laboratory experiments related to the study of corrosion, with special emphasis on dental implants. In situ degradation of a metallic implant is undesirable because it alters the structural integrity of the implant. The issue of corrosion is not limited to a local problem because the particles pmduced as a result could migrate to distant sites, whose evolution would require further studies.

CLIN ORAL IMPLANTS RES. 2011 JUL;22(7):673-680. DOI: 10.1111/J.1600-0501.2010.02081.X. EPUB 2011 JAN 20.

Titanium allergy: could it affect dental implant integration?

Siddiqi A, Payne AGT, De Silva RK, Duncan WJ.

ABSTRACT

PURPOSE:

Degradation products of metallic biomaterials including titanium may result in metal hypersensitivity reaction. Hypersensitivity to biomaterials is often described in terms of vague pain, skin rashes, fatigue and malaise and in some cases implant loss. Recently, titanium hypersensitivity has been suggested as one of the factors responsible for implant failure. Although titanium hypersensitivity is a growing concern, epidemiological data on incidence of titanium-related allergic reactions are still lacking.

MATERIALS AND METHODS:

A computer search of electronic databases primarily MEDLINE and PUBMED was performed with the following key words: 'titanium hypersensitivity', 'titanium allergy', 'titanium release' without any language restriction. Manual searches of the bibliographies of all the retrieved articles were also performed. In addition, a complementary hand search was also conducted to identify recent articles and case reports.

RESULTS:

Most of the literature comprised case reports and prospective in vivo/in vitro trials. One hundred and twenty-seven publications were selected for full text reading. The bulk of the literature originated from the orthopaedic discipline, reporting wear debris following knee/hip arthroplasties. The rest comprised osteosynthesis (plates/screws), oral implant/dental materials, dermatology/cardiac-pacemaker, pathology/cancer, biomaterials and general reports.

CONCLUSION:

This review of the literature indicates that titanium can induce hypersensitivity in susceptible patients and could play a critical role in implant failure. Furthermore, this review supports the need for long-term clinical and radiographic follow-up of all implant patients who are sensitive to metals. At present, we know little about titanium hypersensitivity, but it cannot be excluded as a reason for implant failure.

CLIN IMPLANT DENT RELAT RES. 2013 FEB;15(1):47-52. DOI: 10.1111/J.1708-8208.2010.00330.X. EPUB 2011 MAR 17.

Is titanium sensitivity associated with allergic reactions in patients with dental implants? A systematic review.

Javed F, Al-Hezaimi K, Almas K, Romanos GE.

ABSTRACT

BACKGROUND:
A worrying correlation which seems to be overlooked by clinicians is allergic reactions to titanium (Ti) in patients with dental implants.

PURPOSE:
The aim of the present review study was to assess whether or not Ti sensitivity is associated with allergic reactions in patients with dental implants.

MATERIALS AND METHODS:
To address the focused question "Can Ti cause allergic reactions in patients with dental implants?", databases were explored from 1977 until May 2010 using a combination of the following keywords: "allergy,""dental,""hypersensitivity,""implant,""oral," and "Titanium." Letters to the editor and unpublished data were excluded.

RESULTS:
Seven studies (six clinical and one experimental) were included. The participants were aged between 14.3 and 84.1 years. In five clinical studies, Ti implants were inserted in the mandible. Five studies reported dermal inflammatory conditions and gingival hyperplasia as allergic reactions in patients with Ti dental implants. A case report presented swelling in submental and labial sulcus and hyperemia of soft tissues in a patient with Ti dental implants. Two studies reported that Ti implants are well tolerated in host tissues. The patch test was performed in two clinical studies for the diagnosis of allergic reactions. Memory lymphocyte immunostimulation assay and lymphocyte transformation tests were also performed.

CONCLUSION:
The significance of Ti as a cause of allergic reactions in patients with dental implants remains unproven.

DERMATITIS. 2015 JAN-FEB;26(1):7-25. DOI: 10.1097/DER.0000000000000091.

Hypersensitivity reactions to titanium: diagnosis and management.

Wood MM, Warshaw EM.

ABSTRACT

Titanium is notable for its biocompatibility and is used as biologic implant material across surgical specialties, especially in metal-sensitive individuals. However, rare cases of titanium hypersensitivity reactions are reported in the literature. This article discusses the properties and biological behavior of titanium and provides a thorough review of the literature on reported cases, diagnostic techniques, and approach to management of titanium hypersensitivity.

INT J MOL SCI. 2016 JUN; 17(6): 798. PUBLISHED ONLINE 2016 MAY 24. DOI: 10.3390/IJMS17060798.

Adverse Biological Effect of TiO2 and Hydroxyapatite Nanoparticles Used in Bone Repair and Replacement

Wang J, Wang L, Fan Y.

ABSTRACT

The adverse biological effect of nanoparticles is an unavoidable scientific problem because of their small size and high surface activity. In this review, we focus on nano-hydroxyapatite and TiO2 nanoparticles (NPs) to clarify the potential systemic toxicological effect and cytotoxic response of wear nanoparticles because they are attractive materials for bone implants and are widely investigated to promote the repair and reconstruction of bone. The wear nanoparticles would be prone to binding with proteins to form protein-particle complexes, to interacting with visible components in the blood including erythrocytes, leukocytes, and platelets, and to being phagocytosed by macrophages or fibroblasts to deposit in the local tissue, leading to the formation of fibrous local pseudocapsules. These particles would also be translocated to and disseminated into the main organs such as the lung, liver and spleen via blood circulation. The inflammatory response, oxidative stress, and signaling pathway are elaborated to analyze the potential toxicological mechanism. Inhibition of the oxidative stress response and signaling transduction may be a new therapeutic strategy for wear debris–mediated osteolysis. Developing biomimetic materials with better biocompatibility is our goal for orthopedic implants.

J PERIODONTAL RES. 2017 DEC;52(6):946-954. DOI: 10.1111/JRE.12469. EPUB 2017 JUN 14.

Synergistic interactions between corrosion and wear at titanium-based dental implant connections: A scoping review.

Apaza-Bedoya K, Tarce M, Benfatti CAM, Henriques B, Mathew MT, Teughels W, Souza JCM.

ABSTRACT

Two-piece implant systems are mainly used in oral implantology involving an osseointegrated implant connected to an abutment, which supports prosthetic structures. It is well documented that the presence of microgaps, biofilms and oral fluids at the implant-abutment connection can cause mechanical and biological complications. The aim of this review paper was to report the degradation at the implant-abutment connection by wear and corrosion processes taking place in the oral cavity. Most of the retrieved studies evaluated the wear and corrosion (tribocorrosion) of titanium-based materials used for implants and abutments in artificial saliva. Electrochemical and wear tests together with microscopic techniques were applied to validate the tribocorrosion behavior of the surfaces. A few studies inspected the wear on the inner surfaces of the implant connection as a result of fatigue or removal of abutments. The studies reported increased microgaps after fatigue tests. In addition, data suggest that micromovements occurring at the contacting surfaces can increase the wear of the inner surfaces of the connection. Biofilms and/or glycoproteins act as lubricants, although they can also amplify the corrosion of the surfaces. Consequently, loosening of the implant-abutment connection can take place during mastication. In addition, wear and corrosion debris such as ions and micro- and nanoparticles released into the surrounding tissues can stimulate peri-implant inflammation that can lead to pathologic bone resorption.

INT J MOL SCI. 2018 NOV 13;19(11). PII: E3585. DOI: 10.3390/IJMS19113585.

Potential Causes of Titanium Particle and Ion Release in Implant Dentistry: A Systematic Review.

Delgado-Ruiz R, Romanos G.

ABSTRACT

Implant surface characteristics, as well as physical and mechanical properties, are responsible for the positive interaction between the dental implant, the bone and the surrounding soft tissues. Unfortunately, the dental implant surface does not remain unaltered and changes over time during the life of the implant. If changes occur at the implant surface, mucositis and peri-implantitis processes could be initiated; implant osseointegration might be disrupted and bone resorption phenomena (osteolysis) may lead to implant loss. This systematic review compiled the information related to the potential sources of titanium particle and ions in implant dentistry. Research questions were structured in the Population, Intervention, Comparison, Outcome (PICO) framework. PICO questionnaires were developed and an exhaustive search was performed for all the relevant studies published between 1980 and 2018 involving titanium particles and ions related to implant dentistry procedures. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for the selection and inclusion of the manuscripts in this review. Titanium particle and ions are released during the implant bed preparation, during the implant insertion and during the implant decontamination. In addition, the implant surfaces and restorations are exposed to the saliva, bacteria and chemicals that can potentially dissolve the titanium oxide layer and, therefore, corrosion cycles can be initiated. Mechanical factors, the micro-gap and fluorides can also influence the proportion of metal particles and ions released from implants and restorations.

J DENT RES. 2018 MAR;97(3):259-265. DOI: 10.1177/0022034517740560. EPUB 2017 NOV 12.

Is Metal Particle Release Associated with Peri-implant Bone Destruction? An Emerging Concept.

Fretwurst T, Nelson K, Tarnow DP, Wang HL, Giannobile WV.

ABSTRACT

Peri-implant diseases affecting the surrounding structures of endosseous dental implants include peri-implant mucositis and peri-implantitis. The prevalence of peri-implantitis ranges between 15 % and 20 % after 10 y, highlighting the major challenge in clinical practice in the rehabilitation of dental implant patients. The widespread nature of peri-implant bone loss poses difficulties in the management of biological complications affecting the long-term success of osseointegrated implant reconstructions. Metal and titanium particles have been detected in peri-implant supporting tissues. However, it remains unclear what mechanisms could be responsible for the elicitation of particle and ion release and whether these released implant-associated materials have a local and/or systemic impact on the peri-implant soft and hard tissues. Metal particle release as a potential etiologic factor has been intensively studied in the field of orthopedics and is known to provoke aseptic loosening around arthroplasties and is associated with implant failures. In dental medicine, emerging information about metal/titanium particle release suggests that the potential impact of biomaterials at the abutment or bone interfaces may have an influence on the pathogenesis of peri-implant bone loss. This mini-review highlights current evidence of metal particle release around dental implants and future areas for research.

CLIN ORAL IMPLANTS RES. 2018 OCT;29 SUPPL 18:37-53. DOI: 10.1111/CLR.13305.

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

Mombelli A, Hashim D, Cionca N.

ABSTRACT

OBJECTIVES:
To compile the current evidence regarding the association between the release of titanium particles and biologic complications of dental implants.

MATERIAL AND METHODS:
This is a critical review. We searched the literature using the terms "corrosion," "allergy," "hypersensitivity," or "particles" together with "titanium," "Ti," "TiO2. " The bibliographies of identified publications and previously published review articles were scanned to find additional related articles. We included clinical studies, in vivo and in vitro experiments.

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

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

INT J IMPLANT DENT. 2019 MAR 11;5(1):10. DOI: 10.1186/S40729-019-0162-X.

General review of titanium toxicity.

Kim KT, Eo MY, Nguyen TTH, Kim SM.

ABSTRACT

BACKGROUND:
Titanium is a commonly used inert bio-implant material within the medical and dental fields. Although the use of titanium is thought to be safe with a high success rate, in some cases, there are rare reports of problems caused by titanium. In most of these problematic reports, only individual reports are dominant and comprehensive reporting has not been performed. This comprehensive article has been prepared to review the toxicity of titanium materials within the medical and dental fields.

METHODS:
We used online searching tools including MEDLINE (PubMed), Embase, Cochrane Library, and Google Scholar by combining keywords such as "titanium implant toxicity," "titanium implant corrosion," "titanium implant allergy," and "yellow nail syndrome." Recently updated data has been collected and compiled into one of four categories: "the toxicity of titanium," "the toxicity of titanium alloys," "the toxicity of titanium implants," and "diseases related to titanium."

RESULTS:
Recent studies with regard to titanium toxicity have been increasing and have now expanded to the medical field in addition to the fields of environmental research and basic science. Problems that may arise in titanium-based dental implants include the generation of titanium and titanium alloy particles and ions deposited into surrounding tissues due to the corrosion and wear of implants, resulting in bone loss due to inflammatory reactions, which may lead to osseointegration failure of the dental implant. These titanium ions and particles are systemically deposited and can lead to toxic reactions in other tissues such as yellow nail syndrome. Additionally, implant failure and allergic reactions can occur due to hypersensitivity reactions. Zirconia implants can be considered as an alternative; however, limitations still exist due to a lack of long-term clinical data.

CONCLUSIONS:
Clinicians should pay attention to the use of titanium dental implants and need to be aware of the problems that may arise from the use of titanium implants and should be able to diagnose them, in spite of very rare occurrence. Within the limitation of this study, it was suggested that we should be aware the rare problems of titanium toxicity.