J Indian Prosthodont Soc (Oct-Dec 2012) 12(4):201–207
DOI 10.1007/s13191-012-0139-4

REVIEW ARTICLE

Hypersensitivity to Titanium: A Less Explored Area of Research

Vasantha Vijayaraghavan · Ajay V. Sabane · K. Tejas

Received: 20 May 2012 / Accepted: 22 June 2012 / Published online: 13 July 2012

Abstract Titanium is considered as an excellent biocompatible metal and it is used in implant dentistry. Literature suggests that Ti can induce clinically relevant hypersensitivity and other immune dysfunctions in certain patients chronically exposed to this reactive metal. At the same time, no standard patch test for Ti has so far been developed, and positive reactions to Ti have therefore only rarely been demonstrated with skin testing. This article reports about the corrosion of dental implants, their significance when hypersensitivity is present, and the literature available till date regarding hypersensitivity of titanium.

Keywords Titanium · Corrosion · Hypersensitivity tests · Inflammatory reaction

Introduction

The use of titanium in medicine and dentistry increased during the last three decades. Titanium alloys have been widely used for dental implants, endoprostheses, pacemakers, stents, orthodontal brackets, and eyeglass frames. An oxide film is immediately formed on the surface of this highly reactive transition metal, and this has been claimed to result in good corrosion behavior and high biocompatibility. Within a millisecond of exposure to air, a 10′ oxide layer will be formed on the cut surface of the exposed pure Titanium which will grow to about 100′ thick within a minute. Therefore, Titanium has been considered to be particularly suitable for use in both dental and prosthetic implantation [1]. While numerous issues may arise with the implant following surgery, one of the most fundamentally important is the interaction between the surrounding physiological environment and the surface of the implant itself. This interaction can lead to either the failure of the implant to function as it was intended, or have an adverse effect on the patient. Sporadic cases of intolerance have been reported [2, 3]. These reports raise the question that metal sensitivity may arise after exposure to titanium for some patients in certain circumstances. It has been long recognized that the corrosion products formed as a result of metal–environment interactions have a significant bearing on the biocompatibility and long term stability of the prostheses/implant [4, 5].

V. Vijayaraghavan (✉) · A. V. Sabane · K. Tejas
Department of Prosthodontics, Bharati Vidyapeeth Dental College, Pune, India
e-mail: vijayvasuhome@hotmail.com

General Concepts Related to the Corrosion of Dental Implants

Titanium is a transition metal with an incomplete d-shell in its electronic structure that enables it to form solid solutions with most substitutional elements having a size factor within 20 % (Hume-Rothery's principles for substitutional and interstitial solutions). Titanium has allotropic phase transformation from high temperature beta phase having a body centered cubic structure to room temperature alpha phase having a closely packed hexagonal crystal structure [6]. Titanium alloys with increasing alloying content, exceeding a critical beta value are considered stable beta alloys where no precipitation of the second phase takes place during practical long-time thermal exposure [7]. Human stomatognathus is subjected to varying changes in pH and temperature owing to differences in local, systemic, environmental, economic and social conditions for each

individual. Corrosion can result from the presence of a number of corrosive species like hydrogen ion (H^+), sulfide compounds (S^{2-}), dissolved oxygen, free radicals (O^2, O^-), and chloride ion (Cl^-) resulting in the metal surface breakdown and a consequent adverse tissue reactions [8].

The most common form of corrosion occurring in titanium implants is the galvanic corrosion or dissimilar corrosion. Galvanic coupling of implant to several other metallic restorations may induce one of the several forms of corrosion. Thus coupling remains a great concern for the metallic superstructures covering the implant body. Owing to higher cost of the precious metal alloys (noble alloys) used in prosthodontics, it has led to the development of cost effective semi-precious metallic alternatives (non-noble alloys) like, nickel–chromium, cobalt–chromium, nickel–titanium and several other titanium alloys [9, 10]. An in vivo electrochemical cell is formed and galvanic current causes the corrosion of active metal and the noble metal is protected. The current also passes through the cellular junctions and tissues (desmosomes, hemi-desmosomes and cellular attachments) thereby activating the proprioceptors causing pain. Sensitivity to titanium is characterized by the local presence of abundant macrophages and T lymphocytes and the absence of B lymphocytes, indicating type IV hypersensitivity [11, 12].

When titanium is in the fully passive condition, corrosion rates are typically less than 0.02 mm/year (0.8 mils/year) and well below the 0.13 mm/year (5 mils/year) which is the maximum corrosion rate commonly accepted for biomaterial design and application. This minimal acceptable corrosion rate is primarily due to the finite +4 oxidation of titanium alloys owing to the formation of adherent TiO_2 film although the surface oxide is more complex than a single TiO_2 oxide over their surface.

Crevice Corrosion

Localized crevice corrosion occurs from the geometry of the implant/prostheses assembly. Crevice corrosion testing of titanium implants in function is insidious and very rapid, and may leach several ions into the crevicular space activating the host complement response and causing an adverse reaction that may or may not be tolerated. Titanium alloy implants may be subjected to localized crevice attack exposed to short time periods of hot (>70 °C, or 160 °F) chloride, bromide, iodide, fluoride or sulfate containing solutions during electrosurgery, electro cautery or thermocautery procedures. The reduction in pH and increase in crevicular chloride ion concentration are the essential factors in the initiation and propagation of the pits. When the acidity of the microenvironment around crevice increases with time it dissolves the passive oxide layer thereby causing localized destruction and crevice corrosion [13].

Pitting Corrosion

Localized corrosion attack in an otherwise resistant surface produces pitting corrosion. When the anodic breakdown (pitting) potential of the metal is equal to or less than the corrosion potential under a given set of conditions, spontaneous pitting can be expected. Because of the protective oxide films the titanium implant surface exhibits anodic pitting potential that are very high ($\gg$1 V) compared to other biomaterials used (iron, steel, cobalt–chromium alloys etc.). Thus pitting corrosion is not of much concern in the oral environment for titanium alloys [1].

Fretting Corrosion/Erosion Corrosion

The combination of corrosive fluid (saliva with several enzymes and food particles) and high velocity in the oral environment results in erosion-corrosion or fretting. It is responsible for most of the metal release in tissue. Critical velocities for excessive metal removal depend upon the concentration, shape, and size, hardness of the suspended particles, fluid impingement angle, local turbulence and titanium alloy properties [14]. Titanium alloys exhibit relatively high resistance to fluids containing suspended solids. The typically low concentrations of organic material in oral cavity is of little importance but continuous exposures to local changes around the implant during function can lead to finite removal of the metal as well as the cementing material between the implant and superstructure there by not only promoting erosion corrosion but crevice and galvanic corrosion as well.

Stress Induced Cracking

Stress-corrosion cracking (SCC) is a fracture phenomenon caused by the combined factors of tensile stress, a susceptible alloy, and a corrosive environment. One aspect of SCC is the requirement for the tensile stress to be present, such as those developing from cold work, residual stresses during fabrication/machining, and externally applied functional/occlusal loads. Different surfaces of a metallic restoration (implant or crown structure) may have small pits and crevices and may be differentially exposed to different stresses consequently leading to stress corrosion cracking [15, 16]. The primary idea behind, titanium alloy SCC is the observation that no apparent corrosion, either uniform or localized, usually occurs before the cracking process as a result it is difficult to translate the real oral situation into a laboratory experiment [17].

Mechanisms of Corrosion Resistance

The nature, composition, and thickness of the protective surface oxides that form on titanium alloys depend on environmental conditions. In most oral environments the oxide is typically TiO_2 but may consist of mixtures of other titanium oxides as well including TiO_2, Ti_2O_3, and TiO. High-temperature oxidation promotes the formation of denser, more chemically resistant form of TiO_2 known as rutile, whereas lower temperatures often generate a less crystalline and protective form of TiO_2, called as anatase or a mixture of rutile and anatase [18].

Clinical Significance of Corrosion

95 % of the global use of titanium is not in its metal form, but as titanium dioxide, for its whitening effect (in all kinds of paints and whitening agents), sunscreen properties and use as a safe excipient in the cosmetic, pharmaceutical and food industries [19]. This exposure means our body usually has a titanium content of around 50 ppm [20]. Additionally, the insertion of titanium implants and their permanence in the human body can also cause internal exposure.

Although titanium alloys have better corrosion properties compared to Co–Cr and stainless steel (other implant materials) their corrosion leads to dissolution of titanium and other alloying elements like aluminum, vanadium, niobium, molybdenum etc. [21] causing localized to generalized host response. The leached ions may induce potentially osteolytic cytokines into tissues leading to implant loosening and may even cause severe allergic reactions or hypersensitivity.

Clinical Allergy Studies to Evaluate Hypersensitivity

Hypersensitivity reaction to a metal comes from the presence of ions following ingestion, skin or mucosal contact, or from implant corrosion processes. In their ionic form, metals can be bonded with native proteins to form haptenic antigens, or can trigger the degranulation of mastocytes and basophiles, being capable of developing type I or type IV hypersensitive reactions according to Schramm and Pitto [22, 23].

In Vivo Tests

In a study conducted by Sicillia et al. [24] to evaluate the presence of titanium allergy the selective use of cutaneous and epicutaneous testing were done. Cutaneous tests were performed using the Prick technique, with immediate readings at 10, 20 and 30 min, to assess type I hypersensitivity. Oxide titanium was used in 0.1 and 5 % Vaseline, titanium oxide in 5 % Vaseline and metallic titanium in a 0.1 and 5 % aqueous solution. A drop of the allergen or test substance was placed on the forearm skin surface. The allergen was introduced into the epidermis by means of a lancet puncture. The lancet used in this technique has a 1 mm tip with side stops so that only the tip penetrates the skin. A test was carried out each time with a 0.1 % histamine solution, which serves as a positive control and helps by comparison to interpret the results. Epicutaneous tests were carried out with delayed readings at 24, 48 and 72 h to evaluate type IV hypersensitivity. The study involved the use of titanium oxide in 0.1 and 5 % Vaseline titanium oxide in 5 % Vaseline and metallic titanium in a 0.1 and 5 % aqueous solution. The test substance was deposited on an area of the skin, normally on the back, and covered with a waterproof dressing. The results were read at 24, 48 and 72 h. Vaseline was used as a control. Patch testing in general has been validated only for epidermal antigen contact, may itself induce sensitization of naive T lymphocytes, and is relevant primarily for detecting dermal effects of hypersensitivity (contact dermatitis) [25]. No standard patch test for Ti has so far been developed. But in this study the test substance was applied using patches or test units. These patches have a marked area (at least 0.8 cm^2) in which the antigen is placed. These specific areas can be cellulose, aluminum or plastic. Two types of patches were used: one with a cellulose area with polypropylene insulation, and another with an aluminum area. The titanium aqueous solution was prepared using metallic titanium powder, and its concentration was determined by means of atomic absorption spectrophotometry techniques.

In Vitro Tests

In vitro testing with the lymphocyte transformation test (LTT), on the other hand, can detect both dermally and non-dermally sensitizing allergens (e.g. beryllium). As an in vitro test, LTT cannot sensitize the patient. It has been used successfully to detect hypersensitivity leading to both local and systemic effects, for example those resulting from drug allergies [26, 27].

Lymphocyte transformation tests evaluate lymphocyte competence using in vitro tests to assess the ability of the lymphocytes to proliferate and to recognize and respond to antigens. Two types of lymphocyte transformation tests, mitogens assay and antigen assay are discussed in this policy. The mitogen assay, performed using nonspecific plant lectins, evaluates the mitoric response of T and B lymphocytes to a foreign antigen. In the mitogen assay, a purified culture of lymphocytes from the patient's blood is

incubated with a nonspecific mitogen for 72 h. The culture is then pulse-labeled with tritiated thymidine and can be measured by a liquid scintillation spectrophotometer in counts per minute, which parallels the rate of mitosis. Lymphocyte responsiveness or the extent of mitosis is then reported as a stimulation index, determined by dividing the counts per minute of the stimulated culture by the counts per minute of a control culture. The antigen assay uses specific antigens, such as purified protein derivative (PPD), Candida, mumps, tetanus toxoid and streptokinase, to stimulate lymphocyte transformation. After incubation of 4½ to 7 days, transformation is measured by the same method used in the mitogen assay. In the mitogen and antigen assays, a low stimulation index or unresponsiveness indicates a suppressed or defective immune system [28].

The optimized version of LTT called memory lymphocyte immunostimulation assay (*MELISA*®) [2, 6, 24, 25, 29–31] has also been used for investigating hypersensitivity to Ti in a particular study [29, 30]. The MELISA test has been validated to detect sensitization to titanium and other metals according to Sjekstal, Muller and Valentine-Thon but there can be some lack of specificity in lymphocyte proliferation.

In Vivo Studies Reporting Adverse Reactions

The first cases, in which delayed sensitivity to titanium was suspected, with a local granulomatous reaction, have been described in patients wearing a cardiac pacemaker [32, 33]. In these cases, the diagnosis of a titanium allergy was made with, respectively, a positive patch test with a little square of the pacemaker placed in artificial perspiration, and a positive intra-dermal reaction to an eluate of the surface of the pacemaker.

The intraosseous contact surface is smaller in dental implants than in orthopedic implants [34, 35] and bone has a very low reactivity potential [23]. The oral mucosa and the skin behave very differently from an immunological point of view. In mucosa, the number of Langerhans' cells, which act as antigen-presenting cells, is less as compared to skin [23, 36, 37]. Due to the reduced permeability oral mucosa must be exposed to allergen concentrations 5–12 times greater than the skin in order to cause microscopic reactions. Also contact between the metal and the host is hampered, as the implant and prosthetic structures in the oral cavity are coated with a layer of salivary glycoproteins, which act as a protective barrier [36].

In a study conducted by Sicilia et al. one patient suffered from glottis edema, and this led to admission in the Emergency Department, while two other patients showed cases of spontaneous rapid exfoliation of the implants. 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 [24]. These results are similar to the data obtained in a study carried out with immunologic techniques performed in blood samples, such as the LMI, where a prevalence of 4 % was reached [31]. Data obtained through the MELISA test, carried out on blood samples from patient data banks, shows highly variable results fluctuating from 1.5 to 28 %, possibly overestimating the actual prevalence [30].

There are reports of two cases of de-keratinized hyperplasic reactions of the peri-implant tissues, whose histological characteristics could be compatible with a type IV titanium allergy. The lesions were resistant to treatment; they began to disappear after the titanium abutments were replaced with others made of gold [37].

Loosening of Implants

Several hypotheses have been proposed. Under unfavorable conditions (acidic pH, mechanical friction, close contact to amalgam or gold restorations, etc.). Ti implants may corrode and release ions or micro-particles which can induce inflammation in affected tissues [4, 8, 9, 11, 14]. This mechanism has been suggested to play a role in the loosening of implants [38].

Another clinical report demonstrated the emergence of eczema in association with titanium dental implants. A complete remission was achieved by the removal of the titanium material without oral or topical medications being prescribed. Due to both ethical and practical reasons, a re-exposure of the patient to the suspected titanium allergen was not performed. However, it is noted that the symptoms of eczema temporarily worsened after the removal of the implants. This sudden turn for the worse in the patient's condition suggests that the patient was re-challenged with titanium debris as an allergen during the titanium removal surgery. LTT revealed a specific reaction to $TiCl_3$, $NiSO_4$, and $HgCl_2$ with SI max of 2.39, 2.92, and 32.89, respectively [39].

Nawaz and Wall [40] recently reported on a patient demonstrating a drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, which reflects a serious hypersensitivity reaction to drugs, in association with titanium bioprosthetic implants. Ti implants may corrode and release ions or micro-particles which can induce inflammation in affected tissues [41].

A well documented case of type IV allergy to titanium contained in an osteosynthesis plate inserted for a fracture of the hand was described. The patient had developed

eczema on the hand within a few weeks of the insertion of the plate, and an absence of bone healing. A lymphoblastic transformation blood test (LTT) proved positive, although the patch test for TiO_2 was negative. Following the removal of the plate, the LTT gave negative results and the eczema disappeared [42].

In a study conducted to evaluate titanium release into body organs following the insertion of single threaded screw implants into the mandibles of sheep the concentration of titanium in the nodes of animals with failed implants were seven and 9.4 times higher than the geometric mean of the comparable animals without implant failure. Similarly, the titanium concentration in the lungs of the animals with failed implants was elevated (2.2 and 3.8 times the successful animals), whereas levels in the liver and spleen were ambiguous (a small decrease in one animal and a large increase in the other) [43]. Other investigators have detected titanium infrequently in distant organs of beagle dogs using plasma sprayed titanium implants, although these could be expected to release more titanium due to the nature of the surface [41]. Watterhehn et al. [44] have reported these metal ion release to be associated with carcinogenic and mutagenic activity of the oral cavity.

Fracture of Dental Implant

Fracture of dental implant/prostheses is a very rare phenomenon more often associated with mechanical function and previously use of screw preload systems to clamp flat to flat abutment implant junctions. They can have serious clinical complications. Corrosion can severely limit the fatigue strength and ultimate tensile strength of the material leading to its mechanical failure.

According to Green the end-osseous implant superstructures leached metal ions into the surrounding tissues due to corrosion, leading to fatigue fracture, following 4 years of functional loading into the oral cavity [45]. Yokoyama et al. [46] on the other hand investigated the delayed fracture of titanium implant into the oral environment owing to hydrogen embrittlement and environmentally induced cracking (EIC).

Scope of Research

In a case report of a then ongoing clinical study a patient detected with hypersensitivity to Titanium by MELISA was treated zirconium implants as alternative [47]. Regarding the Zirconium implants till date no long term clinical data has been published. To date, no standard patch test for titanium has so far been developed, and positive reactions to titanium have only rarely been demonstrated with skin testing [48]. The MELISA test has been validated to detect sensitization to titanium and other metals according to Sjekstal et al. 1999, Muller and Valentine-Thon [30], but there can be some lack of specificity in lymphocyte proliferation. Interleukin-17 and Interleukin-22 are produced by a subset of a recently defined T–cell line, known as Th-17. IL-17 has been associated with many inflammatory diseases in humans, including rheumatoid arthritis, organ rejection and asthma. It has been showed that the number of Th-17 cells and the expression of IL-17 were significantly increased in positive patch test biopsies, regardless of the nature of the antigen [49]. IL-22 is a critical mediator in mucosal host defence, which has complex pro-inflammatory and anti-inflammatory and autoimmune effects. It has been shown that patients with contact dermatitis to nickel had a significantly higher IL-22 blood level, compared with control [50], indicating a possible involvement of IL-22 in the pathogenesis of human allergic contact dermatitis. If a blood test is developed to measure the production of IL-17 and/or IL-22 by lymphocytes, it might be helpful to diagnose with certainty a sensitization to titanium. A technique, using flow cytometry to detect the activation of lymphocytes stimulated by a metal, and measuring different mediators (cytokines, inflammatory mediators) released in response to the metal is currently under research [51].

Taking into consideration the few but sure cases of hypersensitivity of titanium, in vitro tests like MELISA can be included as a part of protocol during diagnosis and treatment planning of implant dentistry.

References

1. Bhola R, Bhola SM, Mishra B, Olson DL (2011) Corrosion in titanium dental implants/prostheses: a review. trends biomater. Artif Organs 25:34–46
2. Mitchell DL, Synnott SA, VanDercreek JA (1990) Tissue reaction involving an intraoral skin graft and cp titanium abutments: a clinical report. Int J Oral Maxillofac Implants 5:79–84
3. Katou F, Andoh N, Motegi K, Nagura H (1996) Immunoinflammatory responses in the tissue adjacent to titanium miniplates used in the treatment of mandibular fractures. J Craniomaxillofac Surg 24:156–162
4. Kovacs P, Davidson JA (1996) Chemical and electrochemical aspects of the biocompatibility of titanium and its alloys. In: Brown SA, Lemons JE (ed). Medical application of titanium and its alloys. The material and biological issue, ASTM STP 1272. ASTM, West Conshohocken , pp 63–78
5. Zitter H, Plenk H (1987) The electrochemical behavior of metallic implant materials as an indicator of their biocompatibility. J Biomed Mater Res 21:881–896
6. Joshi VA (2006) Physical metallurgy of titanium alloys. Titanium alloys an atlas of structures and fracture features. CRC Press, pp 7–15
7. Schutz RW (1993) An overview of beta titanium alloys environmental behavior. In: Eylon D, Boyer RR, Koss DA (eds) Beta

titanium alloys in the 1990's. The Mineral, Metals and Materials Society, Warrendale, pp 75–91
8. Bozinni B, Carlino P, Urzo LD, Pepe V, Mele C, Venturo F (2008) An electrochemical impedance investigation of the behavior of anodically oxidized titanium in human plasma and cognate fluids, relevant to dental applications. J Mater Sci Mater Med 19:3443–3453
9. Leinfelder KF, Lemons JE (1998) Clinical restorative materials and techniques. Ler and Febiger, Philadelphia, pp 139–159
10. Lucas LC, Lemons JE (1992) Biodegradation of restorative metallic systems. Adv Dent Res 6:32–37
11. Holgers KM, Roupe G, Tjellstrom A, Bjursten LM (1992) Clinical, immunological and bacteriological evaluation of adverse reactions to skin-penetrating titanium implants in the head and neck region. Contact Dermat 27:1–7
12. Hallab NJ, Mikecz K, Vermes C, Skipor A, Jacobs JJ (2001) Orthopaedic implant related metal toxicity in terms of human lymphocyte reactivity to metal–protein complexes produced from cobalt-base and titanium base implant alloy degradation. Mol Cell Biochem 222:127–136
13. Sato N (1989) Towards a more fundamental understanding of corrosion processes. Corrosion 45:54–368
14. Gat N, Tabakoff W (1980) Effects of temperature on the behavior of metals under erosion by particulate matter. J Test Eval 8:177–186
15. Sprowls DO (1987) Metals handbook, vol 13, corrosion 9th edn. ASM International, Metals Park, pp 222–25
16. Jones DA (1982) Forms of corrosion recognition and prevention. Dillion CP, NACE, Houston, pp 19–43
17. RW Schutz (1992) Stress-corrosion cracking of titanium alloys, stress-corrosion cracking. In: Jones RH (ed) ASM International, pp 265–97
18. Tomashov ND, Altovskii PM (1963) Corrosion and protection of titanium, Government scientific-technical publication of machine-building literature (Russian translation)
19. Weighed P, Geode (2002) Geodynamics and ore deposit evolution. European Science Foundation, Strasbourg
20. Parr GR, Gardner LK, Toth RW (1985) Titanium: the mystery metal of implants dentistry. Dental materials aspects. J Prosthet Dent 54:410–414
21. Rogers SD, Howie DW, Graves SE, Pearcy MJ, Haynes DR (1997) In vitro human monocyte response to wear particles of titanium alloys containing niobium and vanadium. J Bone Joint Surg 79 (B):311–315
22. Hallab N, Merritt K, Jacobs JJ (1997) Metal sensitivity in patients with orthopaedic implants. J Bone Joint Surg Am 83A:428–436
23. Schramm M, Pitto RP (2000) Clinical relevance of allergological tests in total hip joint replacement. In: Willmann G, Zweymüller K (eds) Bio ceramics in hip joint replacement
24. Sicilia A, Cuesta S, Coma G, Arregui I, Guisasola C, Ruiz E et al (2008) Titanium allergy in dental implant patients. Clin Oral Impl Res 19:823–835
25. Okamura T, Morimoto M, Fukushima D, Yamane G (1999) A skin patch test for the diagnosis of titanium allergy. J Dent Res 78:1135
26. Halpern B, Amache N (1967) Diagnosis of drug allergy in vitro with the lymphocyte transformation test. J Allergy 40:168–181
27. Stejskal VDM, Forsbeck M, Nilsson R (1990) Lymphocyte transformation test for diagnosis of isothiazolinone allergy in man. J Invest Dermatol 94:798–802
28. Lymphocyte transformation test. Blue Cross and Blue Shield of Texas, a Division of Health Care Service Corporation, a Mutual Legal Reserve Company, Southwest Texas HMO, Inc. HMO Blue Cross Texas.Independent Licensees of the Blue Cross and Blue Shield Association.med207.093. posted date: 8/22/2003 effective date: 12/1/2003
29. Stejskal V, Cederbrant K, Lindvall A, Forsbeck M (1994) MELISA-An in vitro tool for the study of metal allergy. Toxicol in Vitro 8:991–1000
30. Müller K, Valentine-Thon E (2006) Hypersensitivity to titanium: clinical and laboratory evidence. Neuro Endocrinol Lett 27:31–35
31. Merritt K, Rodrigo JJ (1996) Immune response to synthetic materials. sensitization of patients receiving orthopaedic implants. Clin Orthop Relat Res 326:71–79
32. Peeters MS, Schroeter AL, Van Hale HM, Broadbent JC (1984) Pacemaker contact sensitivity. Contact Dermat 11:218–220
33. Yamauchi R, Morita A, Tsuji T (2000) Pacemaker dermatitis from titanium. Contact Dermat 42:52–53
34. Brunski JB, Puleo DA, Nanci A (2000) Biomaterials and biomechanics of oral and maxillofacial implants: current status and future developments. Int J Oral Maxillofac Implants 15:15–46
35. Akagawa Y, Abe Y (2003) Titanium: the ultimate solution or an evolutionary step? Int J Prosthodont 16(Suppl.):28–29 (discussion 47–51)
36. Bass JK, Fine H, Cisneros GJ (1993) Nickel hypersensitivity in the orthodontic patient. Am J Orthod Dentofacial Orthop 103:280–285
37. Mitchell DL, Synnott SA, VanDercreek JA (1990) Tissue reaction involving an intraoral skin graft and CP titanium abutments: a clinical report. Int J Oral Maxillofac Surg 5:79–84
38. Nakashima Y, Sun D-H, Trindade M, Maloney W, Goodman S, Schurman D et al (1999) Signaling pathways for tumor necrosis factor-α and interleukin-6 expression in human macrophages exposed to titanium-alloy particulate debris in vitro. J Bone Joint Surg 81:603–615
39. Egusa et al (2008) Suspected association of an allergic reaction with titanium dental implants: a clinical report. J Prosthet Dent 100:344–347
40. Nawaz F, Wall BM (2007) Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome: suspected association with titanium bioprosthesis. Am J Med Sci 334:215–218
41. Weingart D, Steinemann S, Schilli W, Strub JR, Hellerich U, Assenmacher J et al (1994) Titanium deposition in regional lymph nodes after insertion of titanium screw implants in maxillofacial region. Int J Oral Maxillofac Surg 23:450–452
42. Thomas P, Brandl W, Majer S, Summer B, Przybilla B (2006) Hypersensitivity to titanium osteosynthesis with impaired fracture healing, eczema and T-cell hyper responsiveness in vitro: case report and review of the literature. Contact dermat 55:199–202
43. Frisken KW, Dandie GW, Lugowski S, Jordan G (2002) A study of titanium release into body organs following the insertion of single threaded screw implants into the mandibles of sheep. Aust Dent J 47:214–217
44. Watterhahn KE, Demple B, Kulesz MM, Copeland ES (1992) Carcinogenesis: a chemical pathology study section workshop, workshop report from the division of research grants, NIH. Cancer Res 52:4058–4063
45. Green NT, Machtei EE, Horwitz J et al (2002) Fracture of dental implants: literature review and report of a case. Implant Dent 11:137–143
46. Yokoyama K, Ichikawa T, Murakami H, Miyamoto Y, Asaoka K (2002) Fracture mechanics of retrieved titanium screw thread in dental implant. Biomaterials 23:2459–2465
47. Oliva X, Oliva J, oliva JD (2010) Full-mouth oral rehabilitation in a titanium allergy patient using zirconium oxide dental implants and zirconium oxide restorations. A case report from an ongoing clinical study. Eur J esthet dent 5:190–203
48. Forte G, Petrucci F, Bocca B (2008) Metal allergens of growing significance: epidemiology, immunotoxicology, strategies for testing and prevention. Inflamm Allergy 7:1–18
49. Oboki K, Ohno T, Saito H, Nakae S (2008) Th17 and allergy. Allergol Int 57:121–134

50. Ricciardi L, Minciullo P, Saitta P, Trombetta D, Saija A, Gangemi S (2009) Increased serum levels of IL-22 in patients with nickel contact dermatitis. Contact Dermat 60:57–58

51. Laurence E (2011) Titanium: a new allergen. Implant dentistry a rapidly evolving practice 531–44. doi:10.5772/19931