CLINICAL ORAL IMPLANTS RESEARCH

Review

Titanium allergy: could it affect dental implant integration?

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Key words: biomaterials, patient centered outcomes, structural biology, tissue physiology

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.

Osseointegration has been described as 'a process in which a clinically asymptomatic rigid fixation of alloplastic material is achieved and maintained in bone during functional loading' (Zarb & Albrektsson 1991). The implication of this discovery has been the use of titanium oral implants by clinicians to replace missing teeth; today such implants have become an essential and predictable treatment for the oral rehabilitation of patients with tooth loss. Although success rates are high, failed implant treatment still presents a significant clinical, psycho-social and financial challenge for clinicians and patient alike (Mardinger et al. 2008). Implant failure during the initial healing period and after osseointegration has been extensively reviewed in the literature (Friberg et al. 1991; van Steenberghe & Quirynen 1993; Esposito et al. 1998a, 1998b; Montes et al. 2007; Alvim-Pereira et al. 2008). Factors including surgical trauma, impaired healing ability, bone characteristics, systemic reasons and implant-related factors have been implicated.

In the main, successful osseointegration has been ascribed to the use of dental implants manufactured from titanium. Titanium has long been regarded as a biocompatible material with high corrosion resistance due to its thin protective oxide (TiO_2 or titania) layer, which spontaneously develops on its surface when exposed to air. Titanium is a non-essential element – no enzymatic pathway has been elucidated that requires titanium as a cofactor. Moreover, there does not appear to be any physiological mechanism for the homeostatic control of titanium (Luckey & Veugapal 1979). Since the 1960s, titanium has developed into a popular metallic biomaterial because of its properties, with many biomechanical applications including arthroplasty, osteosynthesis, pace-maker cases, oral reconstructive procedures, anchorage of bone conductive hearing aids and epistheses as well as jewellery for body piercing. It should be noted, however, that no material can be considered universally biocompatible and this does include titanium (Williams 1994).

Date:
Accepted 23 August 2010

To cite this article:
Siddiqi A, Payne AGT, De Silva RK, Duncan WJ. Titanium allergy: could it affect dental implant integration? *Clin. Oral Impl. Res.* **xx**, 2011; 000–000.
doi: 10.1111/j.1600-0501.2010.02081.x

It is now recognised that environmental factors are a contributing factors in the increasing frequency of allergic disorders affecting world populations (Biologic Markers in Immunotoxicology 1992; Mösges 2002). It is also known that dental biomaterials release substances that alter the oral environment to a varying degree (Schmalz & Garhammer 2002; Müller & Valentine-Thon 2006; Schedle et al. 2007) and thus may contribute to local allergic reactions within the oral tissues. In the oral cavity, an elevated concentration of metal ions may be noxious and act as a local immuno-suppressant (Frisken et al. 2002). Recently, it has been suggested that titanium hypersensitivity may be a factor responsible for implant failure (Okamura et al. 1999; Thomas et al. 2006; Egusa et al. 2008; Sicilia et al. 2008; Mine et al. 2010; Olmedo et al. 2010). Although titanium hypersensitivity is a growing concern, epidemiological data on the incidence of titanium-related hypersensitivity reactions are still lacking.

The precise role of surface chemistry and topography on the early events of osseointegration remain poorly understood (Le Guéhennec et al. 2007). Titanium is a reactive metal with a native oxide film thickness of about 4 nm. After an initial monolayer is formed, further oxide growth occurs. Oxygen ions migrate towards the metal and react with titanium at the base of the oxide layer (Maüsli et al. 1988). The implant–bone interface is dependent in part on the surface characteristics of the implant material (including implant roughness, surface composition and structure), the thickness of the oxide layer and the presence of surface contaminations (Albrektsson 1981; Kasemo 1983). A recent systemic review concluded that the surface topography influences bone response at the micrometre level and even in some cases at nanometre level (Wennerberg & Albrektsson 2009).

Corrosion and allergy to metals

All metallic biomaterials in contact with biological systems undergo degradation called corrosion that results in structural and biological changes in the implanted material itself and in the host tissues, ranging from aseptic implant loosening to bacterial peri-implantitis. Corrosion of metals and alloys used as implants in the body is a complex process and is due to the corrosive environment of the body (Kruger 1979). This chemical process converts metal atoms from a metallic to a non-metallic state. No metallic material is totally resistant to corrosion or ionisation within living tissues. The metals and alloys used as surgical implants achieve passivity by the presence of a protective surface layer. This film inhibits corrosion and keeps current flow and the release of corrosion products at very low level (Kamachi Mudali et al. 2003). Fretting corrosion occurs when two opposing surfaces such as bone plates and the screw heads of a prosthetic device rub each other continuously in an oscillating manner within the body's environment, i.e. small relative movements between contacting surfaces immersed in a corrosive medium. Even in the absence of a corrosive medium, fretting can occur, depositing large amounts of corrosion products within the adjacent tissues (Syrett & Wing 1978; Chaturvedi 2009).

Surface modifications to implanted materials may enhance corrosion resistance but the protective effect is limited because such prostheses are subjected to abrasion and wear, particularly orthopaedic devices (Kamachi Mudali et al. 2003). Ravnholt (1988) demonstrated in an *in vitro* model the detrimental effects of corrosion current and a rise in the pH on titanium by combining it galvanically with dental amalgam. A recent review proposed corrosion as a reason for titanium implant failure (Chaturvedi 2009).

Degradation products of metallic biomaterials including titanium may mediate metal hypersensitivity or allergic reactions (Merritt 1996; Merritt & Rodrigo 1996; Büdinger & Hertl 2000; Hallab et al. 2000; Sicilia et al. 2008; Thomas et al. 2009). Titanium and other elements released from titanium implants have been observed in tissues and organs near implants (Olmedo et al. 2002, 2008). The cause of ion release (other than wear and fretting) from titanium is unclear, as is the precise effect of titanium on human tissues. Possible interactions with tissues have been investigated in the orthopaedic, dermatology and maxillofacial surgery literature (Black et al. 1990; Schliephake et al. 1993; Bianco et al. 1997; Frisken et al. 2002). Released titanium debris (ions) may combine with biomolecules such as native proteins or form a protein-metal complex and become immunogenic, eliciting a Type-IV (T-cell mediated) response. That may cause unexplained pain, troublesome skin rashes, eczema or dermatitis, impaired wound healing and sterile osteomyelitis (Hallab et al. 2001; Thomas 2003). Hypersensitivity reactions have been categorised into four types, as summarised in Table 1.: Types I to III are antibody-mediated, immediate reactions that occurs within minutes as part of the humoral response. Type IV is a cell-mediated, delayed response that occurs hours to days after exposure to the immunogen (Hensten-Pettersen 1993). Immune sensitivity may manifest some distance from the implant, and may even demonstrate a systemic reaction that remains unnoticed or may be incorrectly interpreted (Merritt 1996).

Even though titanium has been regarded as an inert metal, several earlier studies have identified potential haematologic and metabolic toxicity (Carrol & Tullis 1968; Luckey & Veugapal 1979). Reports relating to titanium toxicity are sparse but concur that cationic titanium and soluble titanates are relatively non-toxic in the amounts and forms that are normally ingested, due to poor absorption from the mammalian alimentary tract (Luckey & Veugapal 1979). The purpose of this review is to appraise and critically analyse the medical and dental literature on titanium hypersensitivity with respect to the potential for allergic response to titanium when used as intraosseous devices in oral implantology.

Materials and methods

Internationally published literature addressing implant failures due to hypersensitivity or allergic-reaction-related implant failures and studies examining levels of ion released from implanted materials were included in the review. 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. The literature was screened by one of the authors for relevancy.

Results

This search resulted in 1013 papers (reviews, retrospective studies, prospective *in vitro* studies, RCT's, case reports, abstracts, animal studies) of potential interest. We restricted our search term to titanium hypersensitivity and found 127 relevant publications, which were then selected for full text reading. Most of the literature comprised case reports and prospective *in vivo*/*in vitro* trials. Forty research papers (31%) originated from the orthopaedic discipline and reported on wear debris from prosthesis following knee or hip arthroplasty. The remainder of the retrieved papers could be grouped as follows: metal plates and screws including osteosynthesis devices, oral implants or dental materials (30 papers, 24% of total), dermatology/cardiac-pacemaker (22/17%), pathology/cancer (4/3%), biomaterials (14/11%) and general reports (17/13%). Sixty papers (47%) included discussion of titanium hypersensitivity or allergic reactions: the remainder discussed nickel (Ni), cobalt–chromium (Co–Cr) or gold (Au) and gold alloys. In the current review, each paper was then summarised with respect to hypersensitivity-related dental implant failure.

Table 1. Characteristics of different types of hypersensitivity reactions

Hypersensitivity reaction	Causative factors	Mechanism of hypersensitivity	Typical manifestations	Time course	Induced by biomaterial
Type I (anaphylactic)	Allergic or atopic reaction to external allergens	IgE-mediated activation of basophils and mast cells	Systemic and localised anaphylaxis, hay fever, asthma, unspecific alterations of the skin and mucous membrane	2–30 min	Platinum can induce respiratory allergy. Amalgam allergy has also been reported (a few controversial case reports). Rare possibly dermal allergy due to nickel
Type II (antibody mediated)	Cytotoxic cell-mediated reaction to foreign or self-(autoimmune) antigens	IgG- or IgM-mediated activation of cytotoxic T-cells	Autoimmune haemolytic anaemia, pemphigus, acute rheumatic fever, autoimmune thrombocytopenia purpura	5–8 h	Never documented
Type III (immune complex)	Involves large amounts of circulating antibody specific to an invading antigen.	IgG, IgM	SLE, serum sickness which occurs with nephritis, vasculitis, arthritis and urticaria as well as lymphnode swelling and fever	2–8 h, symptoms can take as long as 14 days to appear	Never documented
Type IV (delayed type)	Cell-mediated hypersensitivity reaction	Involves a complex series of steps that elicit a T-cell response to the antigen	Contact dermatitis, atopic eczema, bullous drug eruptions, tuberculosis, erythema, organ transplant rejection	24–72 h, symptoms can take 14 days to appear	Metals like nickel, cobalt, chromium, titanium, aluminium etc. can cause type IV allergy reactions

Hallab et al. (2000); Hensten-Pettersen (1993).

Orthopaedic and dermatologic literature on titanium/alloy hypersensitivity

There have been several reports of patients suffering from eczematous dermatitis, urticarial rash and adverse local and remote tissue responses, which have been attributed to the presence of an implanted prosthesis (Agins et al. 1988; Black et al. 1990; Jacobs et al. 1998; Beecker et al. 2009). The first report of an allergic reaction to an orthopaedic implant described an eczematous rash over a steel fracture plate (Foussereau & Laugier 1966). Since then, several similar incidences of allergic response to metal prosthesis have been reported.

The core of the literature on metal hypersensitivity involves implants manufactured from alloys containing nickel and cobalt. The prevalence of metal sensitivity among the general population ranges from 10% to 15%, but this increases to 25% in patients with a well-functioning implant (Hallab et al. 2001). A recent study evaluated metal sensitivity by patch testing and lymphocyte transformation tests (LTT) in 16 patients following revision arthroplasty and found an even higher rate (81%) of metal sensitivity (Thomas et al. 2009). These authors suggested that allergic reactions must be included as a differential diagnosis for failed metal-on-metal implants. According to the National Institute of Health Consensus Development Program Conference on Total Knee Replacement (Marciel 2004), the rates of prosthesis failure requiring revision ranges from 10% at 10 years to about 20% at 20 years (approximately 1% per year).

Metal sensitivity is recorded as a contributing factor to failure of the prosthesis in <1% but it is possible that failure to recognise hypersensitivity results in misdiagnosis and under-reporting (Merritt & Rodrigo 1996). Immunological sensitivity to the metallic biomaterials has been suggested as a further cause of implant loosening (Elves et al. 1975). Animal experiments have shown that exposure to metal ions can activate auto-reactive T- and B-cells (Griem & Gleichmann 1995). This metal-induced immuno-suppression was considered an important factor in the development of implant-associated infection in patients with a prosthesis (Wang et al. 1996).

Wear-particle-induced bone loss is hypothesised to be the major factor in late implant loosening (Huber et al. 2009). Lalor et al. (1991) found large quantities of particulate titanium in the peri-implant tissues of five patients who underwent revision surgery for failed hip replacements. They attributed these failures to an allergic response to titanium alloy. In addition to the macrophage reaction to titanium debris (ions), there was also a prominent T-lymphocyte response that suggested Type IV immunological reaction (Lalor et al. 1991). In this non-infective inflammatory process, T-lymphocytes assembled around the implant and initiated osteolysis in the absence of any bacterial infection. Witt & Swann (1991) reported 13 cases of failed total hip replacements and concluded that the tissue reaction in response to metal-wear debris may have contributed to the early failure of these implants. A titanium oxide (TiO_2) surface rapidly reforms in response to wear damage. This process is referred to as 'repassivation' and may produce so much oxide that the surrounding peri-implant tissues turn black (Lalor et al. 1991; Witt & Swann 1991). This metallosis can be dramatic as seen in revision operations, but its biological effects are considered harmless (Konttinen et al. 2005).

Aseptic loosening of articular implants was recently investigated by Huber et al. (2009). Periprosthetic tissue from 11 cases containing unusual solid deposits were analysed under the light microscope. Corrosion products and hypersensitivity-associated tissue reaction were observed, indicating a possible relationship between corrosion development and implant-related hypersensitivity. The hypothesis is that implant-derived wear particles initiate a foreign body inflammatory reaction in the joint capsule and along implant–bone interfaces, which results in bone loss and aseptic loosening. Impairment of soft tissue microcirculation following this reaction may also aggravate osteolysis resulting in early implant failure.

Local or systemic complications such as dermatitis, swelling and pruritius of the skin, following cardiovascular therapeutic interventions have also been reported (Raque & Goldschmidt 1970; Peters et al. 1984; Abdallah et al. 1994; Yamauchi et al. 2000; Freeman 2006; Ishii et al. 2006; Tamenishi et al. 2008). These reactions were interpreted as contact sensitivity to the metal components of the pacemaker casing including nickel, cadmium, cobalt, titanium and polyurethane. Yamauchi et al. (2000) reported a case of allergic reaction to an implanted pacemaker with titanium casing. The patient developed a distinct scaly erythema over the implantation site and later on presented with widespread nummular eczema. In this case, the patch test was negative for titanium. However, titanium sensitivity was confirmed by intracuta-

neous and lymphocyte stimulation testing (Yamauchi et al. 2000). A granulomatous reaction after implantation of a titanium-containing pacemaker (with negative patch test to titanium) was also reported in the literature. The pathophysiology of the granulomatous dermatitis showed a Type histological sections (Viraben et al. 1995).

Skin sensitisation from topical exposure to titanium compounds is very rare. Basketter et al. (2000) reported a case of axillary dermatitis in response to titanium lactate used in a deodorant. Such allergic responses most typically manifest as eczema, urticaria, erythema and pruritis. These reactions hypothetically describe humoral responses of a Type IV cell-mediated hypersensitivity (Hallab et al. 2001).

Titanium particles have been found in human and animal tissues related to titanium osteosynthesis devices (Ferguson et al. 1960; Moberg et al. 1989; Rosenberg et al. 1993; Katou et al. 1996). Thomas et al. (2006) reported a case of impaired fracture healing and eczema localised to the perioperative area, within a few weeks after hand surgery. No patch test reactivity to titanium was found. However, when a LTT was used, the T-lymphocytes showed a marked reactivity to titanium (Thomas et al. 2006). After removal of the titanium material, fracture healing was uneventful.

Kim et al. (1997) in a transmission electron microscopic study, observed local tissue destruction in hard and soft tissues near titanium miniplates and concluded that if the plates remain in situ for a long they may damage adjacent tissues. However, Langford & Frame (2002) did not find any tissue degradation around titanium plates. Most of the titanium particles were extra-cellular, lying within fibrous connective tissue with little or no surrounding cellular reaction. Fretting between the plate and screws during the healing course was suggested as the main cause of titanium release from the plates (Onodera et al. 1993; Schliephake et al. 1993). It has been suggested that the titanium plates should be removed routinely after bone healing (Bos et al. 1990; Schliephake et al. 1993; Katou et al. 1996; Kim et al. 1997). However, some also propose that titanium plates do not have to be removed to avoid local inflammatory problems as there is no evidence to support this hypothesis (Matthew et al. 1996; Theologie-Lygidakis et al. 2007). Nevertheless, compared with the possible risks of a second operation, removal of Ti miniplates should not be a routine procedure except in the case of complaints from patients, particularly in the case of infection, hypersensitivity, dehiscence or screw loosening (Meningaud et al. 2001).

Transport of titanium particles via the lymphatics to the regional lymph nodes has been reported (Onodera et al. 1993), and was considered a major route for dissemination of wear debris (Harmsen et al. 1985; Urban et al. 2000). Elevated levels of the metallic elements have been reported in remote organs such as the spleen, liver, lungs and in body fluids like serum and urine (Ferguson et al. 1962; Heck et al. 1986). Jacobs et al. (1998) reported a three-fold higher serum concentration of metal ions in patients who have had a primary total hip arthroplasty. Case et al. (1994) detected necrosis and fibrosis in the nearby lymph nodes with heavy accumulation of wear debris in three patients.

On the other hand, Bianco et al. (1996) evaluated serum and urine samples at various time points in an animal study and concluded that titanium levels in serum and urine do not increase compared with controls up to 1 year after implantation of titanium fibres. Engh et al. (1997) presented two cases of titanium prosthetic wear debris in remote bone marrow. In each case, histological analysis of bone marrow from the iliac crest revealed macrophages that contained black titanium particles. The inflammatory response to metallic and polymeric debris in lymph nodes has been shown to induce immune activation of macrophages and the associated production of cytokines (Hicks et al. 1996). These potentially osteolytic cytokines include interleukin-1 and tumour necrosis factor-α and are released adjacent to the bone, which contribute to bone resorption through the activation of osteoclasts (Bukata et al. 2004).

A direct association between titanium prosthesis and malignancy has yet to be identified (Gillespie et al. 1988, 1996). Poggio (2007) linked a secondary lesion of plasmacytoma with dental implant failure. He postulated that the titanium surface increased the precursor B-cell population, which expedited the localisation of a new lesion. McGuff et al. (2008) reported a case of low-grade chondroblastic osteosarcoma of the maxilla arising in association with an oral implant. Metal particles were found in the histological specimens of pyogenic granuloma and peripheral giant cell granuloma of two patients with peri-implant mucosal enlargement (Olmedo et al. 2010). The authors suggested titanium particles to be the cause of these reactive lesions. An experimental study demonstrated that wear debris from a worn titanium metal on high-density polyethylene hip replacement produced chromosomal instability and reproductive failure in cell culture (Coen et al. (2003).

Oral implant failure

Loss of osseointegration (implant failure) is an undesirable and often multi-factorial event. Many reasons for implant failure have been reported in the literature (Tonetti & Schmid 1994; Esposito et al. 1998a, 1998b; Mombelli & Lang 1998; Piattelli et al. 1998; Tonetti 1998). It has been postulated that pathologic processes leading to late implant failures may be due to peri-implant infection, biomechanical overload, or a combination of the two (Tonetti & Schmid 1994).

Histopathological observation of 230 failed implants led Piattelli et al. (1998) to suggest four reasons for failure; early and late failures associated with infection, late failures associated with loss of osseointegration in the absence of infection, and late failures due to fracture of the implanted device. Esposito et al. (1998b) systematically reviewed the biological factors and etiopathogenesis of peri-implantitis. They classified implant failure according to biological, mechanical, iatrogenic and patient-related factors. Increased failure rates of up to 15% for dental implants have been reported in smokers (Bain et al. 1993; Moy et al. 2005; Strietzel et al. 2007). Patients who had radiation therapy of the head and neck region were reported to have dental implant failure rates of up to 64% (Granström et al. 1993). Diabetes mellitus has also been reported as an increased risk for implant failure when compared with healthy controls in some studies (Morris et al. 2000; Moy et al. 2005). However, other studies have found no evidence of initial healing problems or diminished clinical success for dental implants in diabetic patients (Smith et al. 1992; Dowell et al. 2007).

Preez et al. (2007) reported a case of suspected implant failure due to titanium hypersensitivity. A severe tissue reaction was localised to the implant site. Histological examination revealed a chronic inflammatory reaction with concomitant fibrosis. Another report associated facial eczema with titanium implant over-denture treatment (Egusa et al. 2008). In both cases, the patients recovered well subsequent to implant removal. Sicilia et al. (2008) in their clinical study of 1500 consecutive implant patients noted that nine had a positive reaction indicating titanium allergy. Five patients had unexplained implant failures, and four patients reported allergic symptoms after implant surgery. One patient suffered from oedema of the glottis and was admitted to emergency care, reflecting the unpredictability of an allergic response to titanium.

Metal sensitivity is conventionally diagnosed using a 'patch-test' where an allergen is applied to the skin for 3–4 days; an erythematous reaction is considered positive. However, because of the exceptional protective and sealing qualities of the skin against direct contact, this test is unreliable as it may give false-positive or false-negative results (Dennis 2001; Nasser 2007). Moreover, sensitization after skin testing has also been reported (Botham et al. 1991; Kimber et al. 2001). There are number of *in vitro* tests available

for metal sensitivity, based on leucocyte migration or proliferation. Müller & Valentine (2006) have reported a study where 56 patients with clinical symptoms after receiving titanium-based implants were investigated using an optimised LTT called Memory Lymphocyte Immuno-Stimulation Assay (MELISA® Medica Foundation, Danderyd, Sweden) and patch testing (Müller & Valentine 2006). The patients were negative to titanium on patch testing. However, patients tested with MELISA® showed a positive response. Of these patients, 21 (37.5%) were positive to Ti allergy, 16 (28.6%) were ambiguous and 19 (33.9%) were negative to titanium. Notably, following the removal of implants, all the 54 patients showed clinical improvement in their allergic symptoms. It should be noted, however, that the MELISA® test is not without controversy. Cederbrant et al. (1997) in an *in vitro* comparative study found no significant differences regarding sensitivity and specificity between MELISA® and conventional LLT. Because of the high number of false-positive results, they concluded that these tests (MELISA® and LLT) are not useful in the diagnosis of metal-related contact allergy (Cederbrant et al. 1997). MELISA® and LTT tests are still under scientific evaluation and are not yet approved as routine tests (Cederbrant et al. 1997; Brehler et al. 1998; Robert-Koch-Institut 2002; Bartram et al. 2006).

Discussion

Our review indicates that reports of allergic reactions to metallic implants and devices are common (Black 1988; Lalor et al. 1991; Hensten-Pettersen 1992). However, the literature on titanium hypersensitivity leading to oral implant failure is scarce, with only four case reports of suspected titanium hypersensitivity and one clinical study, which presented nine patients who were allergic to titanium. We suggest that oral-implant-related titanium-hypersensitivity may be under-reported because of poor understanding or failure to investigate this as a potential aetiological factor.

Metals ions can be released by numerous mechanisms, including corrosion, wear, stress corrosion and corrosion fatigue. Most of the literature on titanium hypersensitivity has focused on the distribution of titanium particles in target organs. Titanium screw-taps and self-tapping titanium fixtures were investigated for ion release during placement in the mandible of mini pigs; it was found that the lungs contained the highest amount of titanium particles (Schliephake et al. 1993). Frisken et al. (2002) in a sheep model observed elevated titanium levels in lymph nodes following aseptic implant loosening. Escape of titanium particles from the implant surface towards the more distal peri-implant tissues has also been reported (Franchi et al. 2007). However, Bianco et al. (1996, 1997) did not find any increase in titanium levels in lungs, spleen and serum/urine concentrations, when titanium fibre felts were implanted into the tibia of rabbits. Surgical handling during implantation and wearing under load were the main causes of metal release from plates and screws implanted in rabbits (Mu et al. 2002). Weingart et al. (1994) studied the deposition of titanium in regional lymph nodes after oral implant placement. They suggested that 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. In the past, such particles have been considered to be of little or no biologic importance.

Pioletti et al. (1999) in an *in vitro* study investigated the cytotoxic effect of different concentrations of commercially pure (cp) titanium particles on osteoblasts. They observed that a higher concentration of titanium wear influences the viability of osteoblasts and these osteoblasts released cytotoxic products. Suppression of extracellular gene expression, reduction in bone-matrix protein production, decreased viability and cellular proliferation and inhibition of mineralisation of the extra-cellular matrix were observed after prolong exposure to cp titanium particles (Kwon et al. 2000; Wang et al. 2002). More recently, Mine et al. (2010) suggested that titanium ions can affect the biological response of cell types that are critical to osseointegration (osteoblasts, osteoclasts and gingival epithelial-like cells). Increased quantities of titanium ions and wear debris have been reported with implants that have a large surface area such as orthopaedic implants (Clarke et al. 2003). Dental implants do not have such large surface areas, which may explain why debris has rarely been observed around failed oral implants (Esposito 2001). Orthopaedic implants also meet the challenge of bearing repetitive load (Weinans et al. 1993). A recent study claimed that titanium-based implant materials contain a small percentage of demonstrable impurities such as Al, Be, Cd, Co, Cr, Cu, Fe, Hf, Mn, Mo, Ni, Pd and V (Harloff et al. 2010). They suggested that these elements can be responsible for the allergic reactions of the different titanium alloys. These results are consistent with those of Schuh et al. (2005) who found 0.012–0.034 wt% of trace elements of nickel in orthopaedic titanium alloys. The orthopaedic literature on metal hypersensitivity helps in understanding biological behaviour. However, it can be questioned whether this knowledge is applicable to dentistry.

Conclusion

This review of the literature indicates that titanium can induce hypersensitivity response in susceptible patients and could play an important role in the failure of titanium oral implants. Furthermore, it seems possible that the incidence of allergic reaction to titanium implants may be under-reported due to a lack of recognition as a possible aetiological factor in implant failure. This review supports the need for long-term clinical and radiographic follow-up of all patients who have had an implant and who are diagnosed with metal sensitivity. At present, we know little about titanium hypersensitivity, but it cannot be excluded as a reason for implant failure.

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