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Review Article

Titanium Allergy- A Less Explored Area in Implant Dentistry

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ABSTRACT

Dental implants have become revolutionized mode of oral rehabilitation in partially and fully edentulous patients. Though there are high success rates in implants, a failure rate of 1.5-6.7% is still existent. Both patient and implant related factors are responsible for implant failure. Among these factors titanium allergy could be responsible for failure of implants in susceptible patients known as "cluster patients". Titanium allergy has been demonstrated by clinical studies and clinical reports. The risk of allergy to titanium is increased in patients who are allergic to other metals. This reminds us not to exclude titanium allergy in susceptible patients. In such patients as a precautionary measure, in vitro tests like "MELISA" can be included as a part of protocol during diagnosis and treatment planning of implant dentistry. This review reports that titanium can induce allergy in susceptible individuals and precautions should be undertaken to avoid the clinical, psycho-social and financial challenge for clinicians & patients.

Introduction

Continued research in diagnostic tools and treatment planning in implant dentistry has improved the quality of life of many of the patients. The use of titanium in medicine and dentistry has increased during last four decades because of its excellent biocompatibility and mechanical properties. Titanium alloys have been widely used for dental implants, endoprostheses, pacemakers, stents, orthodontal brackets, and eyeglass frames, oral reconstructive procedures, anchorage of bone, conductive hearing aids and epistheses as well as jewellery for body piercing.

Although success rates are high (81-85% in maxilla and 98-99% in mandible), a failure rate of 1.5-6.7% is still existent and presents a significant clinical, psycho-social and financial challenge for clinician and patient[1]. Implant failure during initial healing period and after osseointegration has been extensively reviewed in literature[2].Out of various causes of implant failure; allergy or hypersensitivity to dental implant material seems to be least considered and neglected but needs attention. Owing to the excellent properties, titanium has been somewhat surrounded by mysticism in the world of dentistry to

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the extent that there is a general belief, biologically inexplicable, that it cannot cause allergic reactions[3]. It should be noted, however, that no material can be considered universally biocompatible and this does include titanium[4]. Thus, allergy due to titanium might be accountable for the failure of implants in some cases (known as "cluster patients")[5].

PREVALENCE/ INCIDENCE OF ALLERGY TO TITANIUM

Many studies and clinical reports have demonstrated allergy to titanium dental implants.

First case in which delayed sensitivity to titanium was suspected, have been described in patients wearing a cardiac pacemaker[6,7](Peeters et al 1984, Yamauchi et al 200).Another 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.. Following the removal of plate, eczema disappeared[8](Thomas P et al 2006).

CLINICAL MANIFESTATIONS OF ALLERGY TO TITANIUM[12]

Allergic reactions in patients who are sensitive to Ti shows type IV allergy with symptoms ranging from vague pain, skin rashes to implant failure. There will be burning or tingling sensations associated with swelling, oral dryness, or loss of taste. Occasionally more common signs and symptoms (e.g.,headache, dyspepsia, asthenia, arthralgia, myalgia etc).Allergy in the oral cavity manifests as erythema of the oral mucosa, labial edema, purpuric patches on the palate,mouth ulcers, hyperplastic gingivitis, depapillation on the tongue, angular cheilitis,perioral eczematous eruption and lichenoid reactions.

PATHOGENESIS OF TITANIUM ALLERGY

Metals corrode due to interaction with its environment, which results in the release of ions into the surrounding microenvironment. Passivating metals like titanium resist corrosion due to the formation of a surface oxide layer. This layer of metal dioxide forms a boundary at the interface between the biological medium and the metal structure and prevents further deterioration of materials. Even though, Ti is renowned for its high corrosion resistance, possibility of some degree of corrosion of the metal in a biological system cannot be disregarded[13,14].When metal particles/ions are released from the implant surface, they can migrate systemically, remain in the intercellular spaces near the site where they were released or taken up by macrophages[15]. Under hostile circumstances, lower pH phenomenon in a peri-implant region of implant facing extreme mechanical forces, or in the proximity of implant with other metals such as amalgam, gold alloy, or chromium-cobalt alloys, corrosion of Ti may occur. Ti ions or micro particles of Ti released in the area of periodontal tissue adjacent to the implant can cause inflammatory reactions in the surrounding tissues. Type IV delayed-type hypersensitivity is typically associated with implant-related allergic reaction[13].

DIAGNOSIS OF TITANIUM ALLERGY

Allergic test for titanium is suggested in those patients who give a history of allergy to other metals. The most commonly used test is the lymphocyte transformation test (LTT) which is an in vitro method in mucosal sensitizing allergens. Optimized version of LTT is known as memory

lymphocyte immuno stimulation assay (MELISA). Local and systemic effects of hypersensitivity resulting from allergies can be analyzed by this method[10].

TABLE 1. STUDIES & CLINICAL CASE REPORTS SHOWING INCIDENCE OF TITANIUM ALLERGY

Author & Year	Study Design	No. of Subjects	Type of Ti prosthesis worn by patients	Duration of prosthesis insitu	Subjects showing Ti Allergy (%)	Associated Allergy signs	Conclusions from the study
Muller and Valentine-Thon, 2006[10]	Clinical & experimental	56	implants, orthodontic braces or endoprostheses	6 months	37.5% 21 Subjects	Dermatiti & acne-like facial inflammation	Clinically relevant hypersensitivity can be detected in patients with Ti dental implants
Sicilia et al, 2008[11]	Clinical/ Retrospective	1500	Dental implants	3 years	0.6% (9 Subjects)	Redness, urticaria, pruritus, rash, dermatitis and facial eczema	Allergic reactions can be detected in patients with Ti dental implants
Egusa et al. 2008[9]	Case-report	1	2 dental implants	2years	_	Facial eczema with intra ora erythematous lesions	Allergic reactions can be detected in patients with Ti dental implants
Du Preez et al. 2007[16]	Case-report	1	6 titanium implants	1 Week	_	Swelling in submental and labial sulcus, frank pain, hyperaemia of soft tissues	A chronic inflammatory response with fibrosis around all the Ti implants was observed.
Mitchell et al. 1990[17]	Case-report	1 1	4 implants 4 implants	2 Week 3.5 months	_	Gingival hyperplasia Gingival hyperplasia	Clinically relevant hyperplasia in gingival tissues may occur in patients with Ti dental implants
Nawaz, Fareha et al 2007[18]	Case-report	1	Titanium bioprosthesis for a spinal fracture	1 monthn	_	manifestations of hypersensitivity (DRESS) syndrome	

MELISA is a test method developed by Stejskal et al[24] and validated by Valentine-Thon. Patient lymphocytes were tested against TiO2 and nine of following metals beryllium, cadmium, chromium, cobalt , copper , gold , indium , inorganic mercury, lead, nickel , palladium , platinum, and tin. A Stimulation Index (SI) was defined as the quotient of test counts per minute (cpm) and average negative control (background) cpm. SI $\geq$ 3 was considered positive (i.e. indicative of specific sensitization), SI $\geq$ 2 but < 3 ambiguous, and SI < 2 negative. For quality control, morphological analysis was additionally performed to confirm the presence of lymphoblasts in positive reactions and to exclude cytotoxicity in negative reactions[25].However it should also be noted that there are controversies about MELISA test. An in vitro comparative study found no significant difference regarding sensitivity and specificity of MELISAs and LLT and because of the high number of false-positive results it was concluded that these tests may not useful in the diagnosis of metal-related contact allergy. These tests are still under scientific evaluation[26].

DISCUSSION

Since 1960s, titanium has developed into a popular metallic biomaterial because of its excellent properties with various biomechanical applications in field of medicine and dentistry.

It should be noted, however, that no material can be considered universally biocompatible and this does include titanium[4](Williams 1994). It is reported that environmental factors are a contributing in increasing frequency of allergic disorders affecting world populations[19-20] (Biologic Markers in Immunotoxicology 1992; Mo¨sges 2002). It is also known that dental biomaterials release substances that alter the oral environment to a varying degree (Schmalz & Garhammer 2002) and thus may contribute to local allergic reactions within the oral tissues[21].

In previous studies, it was noticed that patients with Ti dental implants demonstrated allergic signs with skin rash, flush and eczema; both intra oral & extra oral signs have been reported. These allergic reactions be entirely due to Ti is a debatable issue. Compared to pure Ti, Ti-alloys (mainly titanium, aluminum, and vanadium alloys) are usually used in implant dentistry because of higher strength[22]. However; small consistent amounts of other elements have been detected in Ti alloys which may act as "impurities." It may therefore be hypothesized that such impurities in the implant material may play a role in triggering allergic reactions in patients with Ti implants[23].

As said there is low prevalence of allergy to Ti, performing a metal allergy assessment in only susceptible patient is required. Thorough medical history taking and clinical examination is essential to identify any allergy to metal[11]. Unfavorable conditions like acidic pH, mechanical friction, proximity of amalgam or gold restorations etc., Ti implants may corrode and release ions or micro-particles which can induce inflammation in peri-implant tissues which is clearly demonstrated in various case reports. This mechanism has been suggested to play a role in failure of implants[27-28].Reports of allergic reactions to metallic bioprosthesis are common, but literature on Ti hypersensitivity leading to dental implant failure is less, with only few case reports and studies of suspected Ti hypersensitivity.

Further studies are required to establish the role of pure Ti dental implants in development of allergic reactions. A sensitive and precise test which will help

PATHOGENESIS OF TITANIUM ALLERGY OCCURS IN TWO WAYS AS FOLLOWS

1) Release of metal ions/particles from implant surface

Ions migrate systemically or taken up by macrophages

Macrophages secretes cytokines responsible for allergic reaction

Initiation of Type IV allergic reaction

2) Titanium ions combines with endogenous proteins to form antigenic molecules

Antigenic molecules are captured by langerhans cells

Langerhans cells present these to T-lymphocytes

Initiation of Type IV allergic reaction

to determine titanium hypersensitivity should be developed[12].

CONCLUSION:

As Ti is gold standard material in the field of medicine and dentistry, taking into consideration the few but sure cases of hypersensitivity of titanium are reported that reminds us not to exclude titanium allergy in susceptible patients who gives history of allergy to metals, in such patients as a precautionary measure, in vitro tests like MELISA can be included as a part of protocol during diagnosis and treatment planning of implant dentistry to avoid complications.

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