Is Titanium Sensitivity Associated with Allergic Reactions in Patients with Dental Implants? A Systematic Review

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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 Letters to the editor and unpublished data were excluded.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.

KEY WORDS: allergy, dental, hypersensitivity, implant, oral, titanium

INTRODUCTION

An allergic or hypersensitive reaction may be defined as acute immunological responses that occur when coming into contact with a known antigen.[1] Hypersensitivity can either be an immediate humoral response (as a result of antibody/antigen complexes of type I, II, and III reactions) or delayed (type-IV) cell-mediated response.[2] Type-IV delayed-type hypersensitivity is usually associated with implant-related hypersensitivity responses which is investigated using skin-testing (in vivo), by lymphocyte transformation testing (LTT), and by leukocyte migration inhibition testing (in vitro).[2]

Several studies[3–8] have reported high implant success rates in healthy as well as medically compromised individuals. Titanium (Ti) alloys are commonly used in implantology because of their high strength, biocompatibility, and corrosion resistance in a physiological environment;[9–11] however, a worrying correlation, which seems to be either overlooked by clinicians or weakly researched upon, is allergic reactions in patients with Ti dental implants.

All metals in contact with a biological environment undergo corrosion which leads to the formation of metallic ions that may trigger the immune system by

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forming complexes with endogenous proteins.[2] Therefore, in order for Ti to tempt an allergic reaction, it must have antigenic characteristics. Tissue analysis from five patients who underwent total hip replacement using Ti implants showed the presence of macrophages, lesser T-lymphocytes, and absence of plasma cells and B-lymphocytes (a characteristic of delayed type IV hypersensitivity reaction).[12] In a study by Huber and colleagues,[13] implants containing corrosive elements (solid chromium orthophosphate corrosion products) were installed in 11 patients. The results demonstrated aseptic loosening of implants in all the patients was associated with the development of immune response in the tissues.[13]

Even though Ti is renowned for its high corrosion resistance, the possibility of some degree of corrosion of the metal in a biological system cannot be disregarded.[14,15] The Holgers study[16] reported cellular inflammatory reactions around bone-anchored percutaneous cochlear Ti implants, indicating an immunological response to the implant material. Ti has also been reported to stimulate bone resorption by inducing differentiation of murine osteoblasts and thus contributing to aseptic loosening of dental implants.[17] Furthermore, Ti has also been reported to cause DNA damage.[18] In a study,[19] the prevalence of Ti allergy in 1,500 consecutive patients with dental implants was investigated.[19] The results confirmed the occurrence of allergic reactions in patients with dental implants; however, the definite incidence of allergic responses to Ti dental implants could not be estimated.

Because the clinical relevance of allergic reactions in patients with Ti dental implants remains debatable, 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

Focused Question

The addressed focused question was: Is Ti sensitivity associated with allergic reactions in patients with dental implants?

Selection Protocol

The selection protocol comprised of the following: (1) original articles; (2) clinical and experimental studies; (3) reference list of potentially relevant original and review articles; (4) intervention: Ti allergy with in patients who have undergone dental implant treatment; and (5) articles published only in the English language.

Letters to the editor, historic reviews, and unpublished data were excluded.

Search Strategy

The authors searched the MEDLINE/PubMed (National Library of Medicine, Bethesda, Maryland) and Google Scholar (advanced search) databases for appropriate articles addressing the focused question. Titles and abstracts of articles that satisfied the selection protocol were screened by the authors and checked for agreement. The full text of the articles judged by title and abstract to be relevant were read and independently assessed against the selection protocol. Databases were searched from 1977 up to and including May 2010 using the following terms in various combinations: "allergy," "dental," "hypersensitivity," "implant," "oral," and "Titanium."

Hand-searching of the reference lists of original and review studies that were found to be relevant in the previous step was performed and once again, any disagreement between the authors was resolved via discussion. The initial search yielded 17 articles. Scrutiny of the titles and abstracts abridged the number of articles to seven[17,19–24] which were processed for data extraction (Table 1). Ten studies, which did not fulfill the selection protocol, were excluded (see Appendix A). Because a limited numbers of original studies have investigated allergic reactions in patients with Ti dental implants, the pattern of the present systematic review was customized to mainly summarize the relevant data.

RESULTS

Characteristics of Included Studies

All studies were conducted either at universities or health-care centers (Table 1). The patients were aged between 14.3 and 84.1 years. Six studies[17,19–23] were clinical and one study[24] had an experimental research design. One study[22] involved both clinical and experimental methods of investigation. Ti implants were inserted in the maxilla and mandible in one[23] and three[17,20,22] clinical studies, respectively. Two clinical reports[19,22] did not mention the jaw locations in which Ti implants were inserted. Six studies[20,23–27] reported the duration for which Ti implants had remained in situ before the investigations which ranged from 1 week to 2 years. There was

TABLE 1 Authors (Year), Study Design, Subject/s, Gender, Number of Titanium Implants Inserted, Duration of Implants In Situ, Subjects with Titanium Allergy, Associated Allergy, and Conclusions of Selected Studies

Authors and Year	Study Design	Subject/s (Mean Age/Range in Years)	Gender	Numbers of Ti Implants Inserted	Duration of Implants in situ	Subjects with Ti Allergy (%)	Associated Allergy	Conclusions
Müller et al. 2006[17]	Clinical and Experimental	56 (53.8/14.3–84.1)	17 M 39 F	NA	6 months	21 (37.5)	Dermatitis and acne-like facial inflammation	Clinically relevant hypersensitivity can be detected in patients with Ti dental implants.
Sicilia et al. 2008[19]	Clinical/ Retrospective	35 (50.2/21–68)	10 M 25 F	NA	NA	9 (0.6)	Redness, urticaria, pruritus, rash, dermatitis and facial eczema	Allergic reactions can be detected in patients with Ti dental implants.
Egusa et al. 2008[20]	Case-report	1 (50-year-old)	F	2	2 years	—	Facial eczema	Allergic reactions can be detected in patients with Ti dental implants.
du Preez et al. 2007[21]	Case-report	1 (49-year-old)	F	6	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.
Flatebø et al. 2006[22]	Clinical/ prospective	13 (41.7/21–69)	6 M 7 F	NA	6 months	—	No allergies reported	No tissue sensitivity reactions to Ti dental implants were revealed.
Torgersen et al. 1995[23]	Experimental	19 (30/16–75)	NA	NA	More than 6 months	NA	No allergies reported	Ti implants are well tolerated by the host.
Mitchell et al. 1990[24]	Case-report	1 (49-year-old)	F	4	2 weeks	1	Gingival hyperplasia	Clinically relevant hyperplasia in the gingival tissues may occur in patients with Ti dental implants.
		1 (44-year-old)	M	4	3.5 months	1	Gingival hyperplasia	

NA = not available; Ti = titanium; M = male; F = female.

no significant difference in gender in terms of allergic reactions in patients with Ti dental implants.

Four studies[17,19–21] showed the development of dermal inflammatory conditions (such as facial eczema, dermatitis, and rashes) in patients in with Ti dental implants; whereas in one study,[24] gingival hyperplasia was reported as an allergic reaction to Ti. Results from a case report[21] reported swelling in submental and labial sulcus, and hyperemia of soft tissues in a female patient with Ti dental implants. Likewise, Mitchell and colleagues[24] presented two cases in their study in which both patients (one female and one male) developed gingival hyperplasia following 2 weeks and 3.5 months of Ti dental implants insertion, respectively. However, two studies[22,23] reported that Ti implants are well tolerated in host tissues.

In one study,[20] metal hypersensitivity was detected using the LTT, whereas memory lymphocyte immunostimulation assay was performed in the study by Müller and colleagues[17] to detect metal hypersensitivity. Epicutaneous (patch) tests were performed in two studies and histological assessment of biopsy tissues obtained from inflamed periimplant tissues was carried out in three studies.[21–23]

DISCUSSION

From the studies that fulfilled our eligibility criteria, it was observed that patients with Ti dental implants presented with allergies such as skin rash, flush and eczema; however, should these allergic reactions be entirely attributed to Ti is a debatable issue. Ti-alloys (chiefly comprising of Ti, aluminium [Al], and vanadium [V]) are usually used in implant dentistry in comparison to pure Ti because of their higher strength.[2] However; small yet 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. In a recent study, Harloff and colleagues[25] used spectral analysis for investigating various Ti implant alloys to determine the percentage of the alloy components and additions that may cause allergic reactions. In this study,[25] various Ti alloys such as sponge Ti, TiAl6V4, and iodide Ti were investigated. The results showed that all the Ti alloy samples contained small yet consistent amounts of other elements such as beryllium (Be), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), nickel (Ni), and palladium (Pa).[25] In the Forte study[26] these elements have been shown to elicit allergic reactions in patients with implants. Schuh and colleagues[27] also reported that the presence of Ni in Ti alloys may induce or exacerbate allergic reactions. Likewise, Al sensitization has been associated with persistent granulomas and recurrent eczema;[28] and Be sensitization has been reported to cause allergies in the oral mucosa.[29] Moreover, a study on guinea pigs reported a delayed skin hypersensitivity reaction in response to challenge with Cu–Be and Al–Be alloys.[30] Similar results have been reported by other studies.[31,32] In short, several impurities have been identified in Ti alloys which may significantly contribute in triggering allergic reactions in patients with dental implants. Further studies, involving pure Ti dental implants are warranted to clarify the role of Ti in the development of allergic reaction in patients with dental implants.

Besides the impact of impurities in Ti alloys, the metals used in prosthetic bridgeworks may also be an incriminating cause for allergic reactions. Ni- and Co-based alloys are widely used in prosthetic dentistry for crown and bridge applications; nevertheless there seems to be no consensus regarding the safety of these alloys. In the study by Garhammer and colleagues[33] patients' oral complaints or symptoms to dental cast alloys were investigated. The results showed that the patients with cast metal alloy prosthesis reported a great variety of subjective complaints including gingivitis, palatal inflammation, lingua plicata, lingua geographica, and lichenoid reactions of the oral mucosa.[33] On the other hand, Lulak and Arikan[34] reported no evidence that dental base metal alloys caused an increase in sensitization.

In conclusion, the significance of Ti as a cause of allergic reactions in patients with dental implants remains unproven.

CONFLICT OF INTEREST AND FINANCIAL DISCLOSURE

The authors declare that they have no conflicts of interest and there was no external source of funding for the present study.

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APPENDIX A: LIST OF EXCLUDED STUDIES. MAIN REASON FOR EXCLUSION IS SHOWN IN PARENTHESES

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