



## TITANIUM ALLERGY IN IMPLANT DENTISTRY : LITERATURE REVIEW

## Dental Science

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## ABSTRACT

Titanium use for making implants to replace the teeth and associated structures is now in common Dental practice. Owing to its high resistance to corrosion in a physiological environment and the excellent biocompatibility that gives it a passive, stable oxide film, titanium is considered the material of choice for intraosseous use. There are certain studies which show titanium as an allergen but the resources to diagnose titanium sensitivity are very limited. The allergic response to titanium is reported in very few cases. The purpose of this article is to create awareness among the people handling and using titanium in dentistry so that better strategies can be developed to manage the allergic response to it.

## KEYWORDS

Titanium, Memory Lymphocyte immune-stimulation assay test, Patch test, Blood test, Lymphocyte-transformation test.

## INTRODUCTION:

Dentists have used implants to improve patient's dental aesthetics, health and function for decades. The use of titanium in dentistry increased during last three decades. Given its high resistance to corrosion in a physiological environment & the excellent biocompatibility that gives its passive stable oxide film titanium is considered the material of choice for intraosseous use in medical field<sup>1</sup>.

Titanium to provoke an allergic reaction must have antigenic properties and must be in contact with the organism. The insertion of titanium implants and their permanence in the human body enhances the amount of internal exposure and it has been proven that titanium ion concentration tissue surrounding dental implants as well as in regional lymph nodes and pulmonary tissue.

## Allergic reaction to Titanium

There are studies of proving titanium allergy, **Abraham ET al<sup>2</sup>**. Demonstrated the presence of titanium in saliva and gingival fluid of patients carrying titanium dental implants. According to the authors, the highest titanium levels corresponded to patients carrying implants over longer periods of time, thus indicating that titanium accumulates in peri-implant gingival tissue.

There are several case reports in the literature that describe histologic evidence of inflammatory response and the presence of metallic ions/particles in the tissues adjacent to orthopaedic prostheses of titanium or titanium-based alloys<sup>3</sup>.

In addition, some studies have evaluated tissue response of human oral mucosa adjacent to titanium cover screws and found metal particles in the tissues studied; such particles may have been the result of electrochemical corrosion<sup>4</sup>.

**Lim ET al.Studied<sup>5</sup>** allergic contact stomatitis caused by titanium nitride-coated implant abutment Study clearly dictates the incidence of allergic contact stomatitis due to titanium nitride-coated implant abutment.

Hypersensitisation is defined as an excessive immune reaction that occurs when coming into contact with a known antigen<sup>6</sup>. In their ionic form, metals can be bonded with native protein to form haptic antigens, or can trigger the degranulation of mastocytes and basophiles being capable of developing Type I or type IV hypersensitive reactions<sup>7,8</sup>.

Type I or IV reactions can occur after placing permanent metal dental implants in allergic patients. There are numerous symptoms that have

been seen which may range from skin rashes and implant failure, to non-specific immune suppression. Although we know that titanium allergy is uncommon and that not all patients sensitized to a metal display complications following an endosseousimplant<sup>9</sup>.

Most of the evidence for titanium sensitivity comes from orthopaedic research but its relevance to dentistry must be inferred with great caution. The oral mucosa has different immunological properties than the skin like it is less permeable, contains fewer Langerhans's APCs and is coated by salivary glycoproteins. It has been proposed that oral mucosa must be exposed to allergen concentrations 5–12 times greater than the skin in order to invoke the same stimulus level. Ti allergy can be detected in dental implant patients, even though its estimated prevalence is low (0.6%). A significantly higher risk of positive allergic reaction was found in patients showing post-op allergy compatible response (ACRG), in which cases allergy tests could be recommended<sup>10</sup>.

Before implant placement, it has been shown that many patients suffer from multiple allergies and that people with a history of allergy to metals and jewellery have greater risk of hypersensitivity reaction to a metal implant<sup>11</sup>. Furthermore, although titanium allergy has a low prevalence rate, for patients with a previous history of allergies, it may be advisable to carry out a metal allergy assessment and allergy testing before placing permanent implants, in order to avoid a failure of the implant due to an allergic reaction to titanium.

After implant placement the failure of implants has been widely studied, and the main causes of dental implant failure are infection and overload<sup>12,13</sup>. However, some failures are difficult to explain, such as spontaneous rapid exfoliation of the implant, or the successive failure of implants in the same patients, known as "cluster phenomenon", without any infection or overload risk factor identified. Authors agree that in these cases, there must be a systemic determinant of failure that has not been identified or understood<sup>14,15</sup>. An allergic reaction can be reasonably suspected after dental implant placement, on the basis of signs or symptoms associated with allergy, such as rash, urticaria, pruritus, swelling in the orofacial region, oral or facial erythema, eczematous lesions of the cheeks or hyperplastic lesions of soft tissue (the peri-implant mucosa)<sup>16</sup>. In these cases, allergy testing should be performed.

There are different kind of diagnostic tests to detect the titanium allergy. Epicutaneous tests (patch tests), skin test (prick test) for diagnosing Type I allergy, the lymphocyte transformation test (LTT) is applied by an in vitro method in mucosal sensitizing allergen. The

optimized version of LTT is known as Memory Lymphocyte Immuno Stimulation Assay (MELISA). Local and systemic effects of hypersensitivity resulting from allergies can be analysed by this method<sup>17,18</sup>.

There can be various manifestations of titanium allergy such as burning or tingling sensations, generally associated with swelling, oral dryness, or loss of taste<sup>19</sup>, or 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 oedema, or purpuric patches on the palate, mouth ulcers, hyperplastic gingivitis, depapillation on the tongue, angular cheilitis, perioral eczematous eruption, or lichenoid reactions<sup>20</sup>.

#### Diagnostic test for Titanium allergy

##### Memory lymphocyte immuno-stimulation assay test

The MELISA test has been validated to detect sensitization to titanium and other metals<sup>21</sup>, but there can be some lack of specificity in lymphocyte proliferation. It would be valuable to have a sensitive and specific test that could help in the diagnosis of titanium sensitization or allergy.

##### Patch test

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<sup>22</sup>. The sensitivity of patch tests has been shown to be about 75% for type IV metal allergy. Some authors have suggested that 0.1% and 0.2% titanium sulphate solution and 0.1% and 0.2% titanium chloride are successful reagents for the skin-patch tests and could be a valuable alternative to the titanium oxide normally used for patch testing<sup>23</sup>, but so far no study related to dental implants allergies has used the method.

##### Blood test

Helps in the diagnosis of a type IV allergy.

##### Lymphocyte transformation test

In vitro testing with the Lymphocyte transformation test (LTT) measure lymphocyte proliferation following contact with an allergen is based on the tritiated thymidine incorporation by lymphocytes. Some authors report that there could be that non-relevant proliferation of lymphocytes happen in non-sensitized patients, leading to some false-positive results.

## DISCUSSION

Titanium is currently being used routinely in the manufacture of dental and orthopaedic implants due to its excellent biocompatibility. Biocompatibility is defined as the ability of a material to perform with an appropriate host response in a specific application<sup>24</sup>.

No metal or alloy is completely inert in vivo. However, as the oral cavity serves as an ideal environment for corrosion, any metal may corrode to some extent in spite of being highly biocompatible. All metals will undergo a slow removal of ions from the surface, largely because of local and temporal variations in microstructure and environment. As the use of titanium is increasing to a great extent in dentistry it is absolutely necessary to have a detailed knowledge of the material<sup>25</sup>.

Investigations have been carried out about hypersensitivity reactions with titanium. The intraosseous contact surface is smaller in dental implants than in orthopedic ones, which may be particularly important considering that bone has a very low reactivity potential. On the other hand, oral mucosa and the skin behave very differently from an immunological point of view, partially because of the influence of specific immune systems for each organ, such as skin-associated lymphoid tissue and mucosa-associated lymphoid tissue. A practical application is that, in mucosa, the number of Langerhans' cells, which act as antigen-presenting cells, is much smaller<sup>26</sup>. It is because of this, and perhaps also because of its reduced permeability, that oral mucosa must be exposed to allergen concentrations 5-12 times greater than the skin in order to cause tissue microscopic reactions. Moreover, 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 glycoprotein, which act as a protective barrier<sup>27</sup>.

It is important to recognize the difference between the presence of immunocompetent cells in tissues and clinical features consistent with hypersensitivity. In the future, our understanding of titanium allergy

would be advanced by a comparison of histologic features in symptomatic and asymptomatic patients with titanium implants in the maxillofacial region. Sensitivity to titanium is characterized by the local presence of abundant macrophages and T lymphocytes and the absence of B lymphocytes, indicating Type 4 hypersensitivity.

Researches are going on to develop a technique using flow cytometry, for the purpose of detecting the activation of lymphocytes stimulated by a metal.

## CONCLUSION

Improvements in health care and increased life expectancy of the population demand the design of implant biomaterials demonstrating no or minimal deleterious effects on host tissues. Studies show that Titanium acts as a potential allergen, so diagnostic tests are mandatory before implant placements and more stress should be given to find new diagnostic tests.

## REFERENCES

- Smith D, Lugowski S, Mchugh A, Deporter D, Watson P, Chipman M. Systemic metal ion levels in dental implant patients. *Int J Oral Maxillofac Implants* 1996;12:828-34.
- Abraham JA, Greno'n MS, Sa'nechez HJ, Pe' rez CA, Valentinuuzzi MC. Titanium Based Implants, Metal Release Study in the Oral Environment. Laboratorionacional de LuzSi'ncrotron. Activity report. Sa'oCarlos, Brazil: Brazilian Synchrotron Light Laboratory;2006:1-2.
- Jacobs JJ, Gilbert JL, Urban RM. Corrosion of metal orthopaedic implants. *J Bone Joint Surg Am* 1998;80:268-282.
- Olmedo DG, Paparella ML, Spielberg M, Brandizzi D, Guglielmotti MB, Cabrini RL. Oral mucosa tissue response to titanium cover screws. *J Periodontol* 2012;83:973-980.
- Lim H, Lee K, Koh Y, Park S. Allergic contact stomatitis caused by a titanium nitride-coated implant abutment: A clinical report. *J Prosthet Dent* 2012;108:209-13.
- Roitt IM, Delves PJ. *Essential Immunology*. 10th ed. London: Blackwell Science Ltd;2001
- Schramm M, Pitto RP. Clinical relevance of allergological tests in total hip joint Replacement. In: Willmann G, Zweymuller K, editor. *Bioceramics in Hip joint replacement* New York, USA: Thieme; 2000. p. 101-6.
- Hallab N, Merritt K, Jacobs J. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am* 2001;83:428-36.
- Tamai, K., Mitsumori, M., Fujishiro, S., Kokubo, M., Ooya, N., Nagata, Y., Sasai, K., Hiraoka, M. & Inamoto, T. A case of allergic reaction to surgical metal clips inserted for Postoperative boost irradiation in a patient undergoing breastconserving therapy. *Breast Cancer* 2001; 8: 90-92.
- Sicilia A, Cuesta S, Coma G, Arregui I, Guisasaola C, Ruiz E, Maestro A. Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients. *Clin. Oral Impl. Res.* 19, 2008; 823-835.
- Hallab M, Mikecz K, Vermes C, Skipor A, Jacobs J. Differential lymphocyte reactivity to Serum-derived metal-protein complexes produced from cobalt-based and titaniumbased Implant alloy degradation. *J Biomed Mater Res* 2001;56:427-36.
- Esposito M, Hirsch J, Lekholm U, Thomsen P. Differential diagnosis and treatment Strategies for biologic complications and failing oral implants: A review of the literature. *Int J Oral Maxillofacial Implants* 1999;14:473-90.
- Esposito M, Thomsen P, Ericson L, Lekholm U. Histopathologic observations on early oral Implant failures. *Int J Oral Maxillofacial Implants* 1999;14:798-810.
- Wood M, Vermilyea S. A review of selected dental literature on evidence-based treatment Planning for dental implants: Reports of the committee on research in fixedprosthodontics Of the academy of fixed prosthodontics. *J Prosthet Dent* 2004;94:447-62.
- Chuang S, Cai T, Douglass C, Wei L, Dodson T. Frailty approach for the analysis of Clustered failure time observation in dental research. *J Dent Res* 2005;84:54-8.
- Mitchell DL, Synnott SA, Van Dercreek JA. Tissue reaction involving an intraoral skin Graft and CP titanium abutments: A clinical report. *Int J Oral Maxillofac Implants* 1990;5:79-84.
- Stejskal VD, Cederbrant K, Lindvall A, Forsbeck M. MELISA-an in vitro tool for the study Of metal allergy. *Toxicol In Vitro*. 1994;8(5): 991-1000.
- Müller K, Valentine-Thon E. Hypersensitivity to titanium: clinical and laboratory evidence *Neuro Endocrinol Lett*. 2006;27 Suppl 1:31-35.
- Okamura T, Morimoto M, Fukushima D, Yamane G. *J Dent Res*. 1999;78:1135.
- Lygre GB, Gjerdet NR, Grønningsaeter AG, Björkman L. Reporting on adverse reactions To dental materials: intraoral observations at a clinical follow-up. *Community Dent Oral Epidemiol*. 2003;31(3):200-206.
- Müller K, Valentine-Thon E. Hypersensitivity to titanium: Clinical and laboratoryevidence *Neuro Endocrinol Lett* 2006;27:31-5.
- Forte G, Petrucci F, Bocca B. Metal allergens of growing significance: Epidemiology, Immunotoxicology, strategies for testing and prevention. *Inflamm Allergy* 2008;7:1-18.
- Okamura T, Morimoto M, Fukushima D, Yamane G. A skin patch test for the diagnosis of Titanium allergy. *J Dent Res* 1999;78:1135.
- Williams D. Definitions in Biomaterials, Proceedings of a Consensus Conference of the European Society for Biomaterials, ISBN 044428585, Chester, England, 1986: 3:87-89.
- Chaturvedi TP Allergy related to dental implant and its clinical significance *Clinical, Cosmetic and Investigational Dentistry* 2013;5:57-61.
- Schramm M, Pitto RP. Clinical relevance of allergological tests in total hip joint Replacement. In: Willmann G, Zweymuller K, editor. *Bioceramics in Hip joint replacement*. New York, USA: Thieme; 2000. p. 101-6.
- Bass JK, Fine H, Cisneros GJ. Nickel hypersensitivity in the orthodontic patient. *Am J Orthod Dentofacial Orthop* 1993;103:280-5.