

Titanium implants - testing for allergy

Titanium has traditionally been seen as a “biocompatible metal” which osseointegrates with bone, which is why it is used in dental surgery as well as orthopaedic surgery. The prevalence of titanium allergy is difficult to assess, because of uncertainty in the methods of detection [1]. The risk and prevalence of allergy to titanium has been much discussed [2]. There are extremely low rates of positive patch test reactions to titanium salts (particularly TiO_2) [3], however there are increasing numbers of case reports describing adverse reactions to titanium and to titanium-based alloys [2,4,5,6].

Allergic potential of titanium

When titanium is exposed to air it produces a stable oxide film, however *in vivo* studies have proved that metal ions are released into fluids and tissue. In the oral cavity, there are additional factors which could lead to increased metal release, such as infection, bacterial load (*lipopolysaccharides*), fluoride containing toothpastes and acidic foods [1]. Some researchers believe that titanium allergy is complicated by the fact that patients may be reacting to impurities found in titanium [4], for example nickel, chromium and cadmium.

MELISA and titanium allergy patch testing

Studies show that lymphocyte transformation tests are better suited for diagnosing possible metal sensitivity than traditional patch testing. Implant-related hypersensitivity reactions are mediated by sensitized T cells [8] and the relationship between skin hypersensitivity and systemic hypersensitivity is ill defined [8,9]. Lack of standardization in patch testing may also contribute to reduced reliability [10,11]. The accuracy of patch testing for titanium allergy in particular seems to be variable; Mayo clinic failed to find any positive reactions to titanium in over a decade [3], despite several published cases of titanium allergy [2,4,5,6]. Titanium has been shown to induce clinically relevant hypersensitivity which can be detected with MELISA testing [12,13]. Some surgeons suggest MELISA testing prior to surgery in patients with suspected metal allergy [14]. This allows the surgeon to choose the most compatible implant material.

Failure rates and clusters

Whilst not all allergic patients experience implant failure, the failure rates are relatively high. The largest study of 4,716 patients and over 11,000 implants took place in Sweden. The study shows that implant loss occurred in 7.6% of all patients over a follow-up of 9 years. Additionally 14.5% of all patients exhibited moderate/severe peri-implantitis [15]. Others studies have indicated potential failure rates as high as 26% [16].

Implant failures are not randomly distributed but occur in specific high-risk groups and individuals [17]. Whilst smoking and advanced age are considered high risk, very little work has been conducted on allergy and risk. Failure of implants may be used as an indicator of titanium allergy once infection has been ruled out [9,18]. Given the difficulties of diagnosing titanium allergy, studies probably underestimate the true prevalence of titanium allergies in patients [1,4].

MELISA testing

MELISA is an optimised, clinically validated lymphocyte transformation test (LTT) with improved specificity and sensitivity. LTTs are used extensively to detect type IV allergies to metals and drugs. For testing prior to implantation, a panel of the 5 most commonly found metals in dental implant surgery is available. The lymphocyte reaction to metals is measured by two separate methods: uptake of radioactive thymidine by dividing lymphocytes and the evaluation of cellular stimulation by microscopy.

Clinical and laboratory evidence

In research conducted by Dr Valentine-Thon, 56 patients with various clinical symptoms after receiving titanium-based implants were tested for allergy. None showed a positive patch test results for titanium. In MELISA testing of TiO_2 , 21 (37.5%) were positive with an average Stimulation Index (SI) of 6.3, 16 (28.6%) were ambiguous, with an average SI of 2.4. All patients who had their implants removed showed a clinical improvement. [12]



What are the symptoms of titanium allergy?

There is a wide range of symptoms connected to titanium allergy, and not everyone gets all the symptoms. Below are some of the symptoms which were listed in the article *Hypersensitivity to titanium: Clinical and laboratory evidence* as being reported by patients with titanium allergy:

- muscle, joint, and nerve pain
- chronic fatigue syndrome (CFS)
- neurological problems
- depression
- multiple chemical sensitivity (MCS)
- dermatitis, and acne-like facial inflammation
- headaches [12]

These symptoms may develop slowly over a period of several months. It has been shown that many patients suffer from multiple allergies [11], and that people with a history of allergy to metals or jewellery have a greater risk of developing a hypersensitivity reaction to a metal implant [8].

Impurities/alloys in titanium implant materials

1. Pure titanium is composed of about 99% titanium. Traces of other metals such as nickel, chromium, cobalt and aluminium are found even in commercially pure titanium due to the production process [7,12,19,20].
2. The titanium alloy most commonly used in implants is Ti-Al6-V4.

Alternatives for metal hypersensitive patients

Zirconium oxide (Zirconia) dental implants may be used in patients with known metal allergies. [22,23]

Testing procedure

A blood sample can be sent to any licensed MELISA laboratory. Samples are time sensitive and should arrive within 24hrs (maximally 48hrs). The blood sample should be kept at room temperature and sent in sodium citrate light blue Vacuette tubes. The amount of blood required depends on how many antigens are to be tested.

For adults, a screening of 10 metals, 36 ml (or 4 large 9ml tubes) of blood is needed.

Taking steroids or other immunosuppressant drugs may affect the test results.

A questionnaire which helps to identify patients who are likely to benefit from MELISA testing can also be provided and evaluated. However, patient history alone is not sufficient to diagnose metal hypersensitivity [21].

References

- [1] Fage SW, Muris J, Jakobsen SS, Thyssen JP. Titanium: a review on exposure, release, penetration, allergy, epidemiology, and clinical reactivity. *Contact Dermatitis*. (2016), 74: 323–345. doi:10.1111/cod.12565
- [2] Wood MM, Warshaw EM. Hypersensitivity reactions to titanium: diagnosis and management. *Dermatitis* 2015; 26: 7–25.
- [3] Davis MD et al. Patch testing with a large series of metal allergens: findings from more than 1,000 patients in one decade at Mayo Clinic. *Dermatitis*. 2011 Sep-Oct;22(5):256-71.
- [4] Evrard L, Waroquier D, Parent D. Allergies to dental metals. Titanium: a new allergen. *Rev Med Brux*. 2010 Jan-Feb;31(1):44-9.
- [5] Basko-Plluska J, Thyssen JP, Schalock P. Cutaneous and Systemic Hypersensitivity Reactions to Metallic Implants. *Dermatitis*. 2011;22(2):65-79.
- [6] Thomas P. (2014). Clinical and diagnostic challenges of metal implant allergy using the example of orthopaedic surgical implants: Part 15 of the Series Molecular Allergology. *Allergo Journal International*, 23(6), 179–185. <http://doi.org/10.1007/s40629-014-0023-3>
- [7] Harloff T, Hönle W, Holzwarth U, Bader R, Thomas P, Schuh A. Titanium allergy or not? "Impurity" of titanium implant materials. *Health*, Vol.2 No.4, April 2010.
- [8] Hallab N, Merritt K, Jacobs J. Metal sensitivity in patients with orthopedic implants. *The Journal of Bone and Joint Surgery* 2001;83:428.
- [9] 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.
- [10] Fischer LA, Johansen JD, Menné T. Methylidibromoglutaronitrile allergy: relationship between patch test and repeated open application test thresholds. *Br J Dermatol*. 2008 Nov;159(5):1138-43.
- [11] Forte G, Petrucci F, Bocca B. Metal allergens of growing significance: epidemiology, immunotoxicology, strategies for testing and prevention. *Inflamm Allergy Drug Targets*. 2008 Sep;7(3):145-62.
- [12] Müller K, Valentine-Thon E. Hypersensitivity to titanium: Clinical and laboratory evidence. *Neuroendocrinology Letters Volume 27 Suppl. 1* 2006; 27(Suppl 1):17-24.
- [13] Valentine-Thon E, Müller K, Guzzi G, Kreisel S, Ohnsorge P, Sandkamp. LTT-MELISA® is clinically relevant for detecting and monitoring metal allergy. *Neuro Endocrinol Lett* 2006; 27(Suppl 1): 17-24.
- [14] <http://www.mcmincentre.co.uk/ceramic-birmingham-mid-head-resection.html>
- [15] Derks J, Håkansson J, Wennström JL, Klinge B, Berglundh T. Patient-reported outcomes of dental implant therapy in a large randomly selected sample. *Clin Oral Implants Res*. 2015 May;26(5):586-91. doi: 10.1111/clr.12464
- [16] Bandeira de Almeida A, Prado Maia L, Ramos UD, Scombatti de Souza SL, Bazan Palioto D. Success, survival and failure rates of dental implants a cross-sectional study. *J Oral Science Rehabilitation*. 2017 Jun;3(1):24–31.
- [17] Jemt T, Hager P. Early complete failures of fixed implant supported prostheses in the edentulous maxilla: a 3-year analysis of 17 consecutive cluster failure patients. *Clin Implant Dent Relat Res*. 2006;8:77-86
- [18] 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 fixed prosthodontics of the academy of fixed prosthodontics. *J*
- [19] Schuh A, Thomas P, Kachler W, Goske J, Wagner L, Holzwarth U, Forst R. Allergic potential of titanium implants. *Orthopäde*. 2005 Apr;34(4):327-8, 330-3.
- [20] Darvell, BW et al. Contamination of titanium castings by aluminium oxide blasting. *J Dent*. 1995 Oct;23(5):319-22
- [21] Niki Y, Matsumoto H, Otani T, Yatabe T, Kondo M, Yoshimine F, Toyama Y. Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. *Biomaterials*. 2005;26(9):1019-26.
- [22] Sivaraman K et al. Is zirconia a viable alternative to titanium for oral implant? A critical review. *J Prosthodont Res*. 2017 Aug 17. pii: S1883-1958(17)30078-6. doi: 10.1016/j.jpor.2017.07.003.
- [23] Oliva X et al. Full-mouth oral rehabilitation in a titanium allergy patient using zirconium oxide dental implants and zirconium oxide restorations. *Eur J Esthet Dent*. 2010 Summer;5(2):190-203.

MELISA Diagnostics Ltd

t +44 20 8133 5166 f +44 20 8711 5958 e info@melisa.org w www.melisa.org

