Identifying and diagnosing patients with metal hypersensitivity

The incidence of total joint arthroplasty (TJA) procedures is increasing [1]. As a considerable number of patients undergoing TJAs have metal sensitivity and may react to their prosthesis, the incidence of metal sensitivity leading to implant failure is also likely to increase [2].

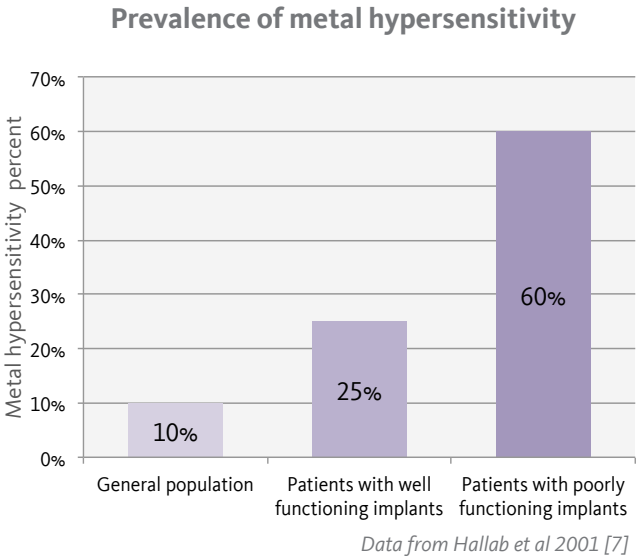
Patients suffering from metal hypersensitivity may have local symptoms associated with an overactive immune response such as localised pain, swelling, cutaneous allergic reactions, joint and muscle pain, implant failure or recurrent suspected infections around the operation site. Also, systemic reactions such as fibromyalgia and chronic fatigue can be exacerbated or triggered by metal hypersensitivity.

MELISA is a clinically validated blood test [3] that can detect type-IV cell-mediated allergy to multiple metals and certain components of bone cements. Metal ions released through implant corrosion bind to proteins in the body. In some patients, metal haptens can trigger an overagressive immune response, which may lead to clinical complications.

MELISA may be used in two ways for orthopaedic patients with suspected metal hypersensitivity:
First, before surgery, patients with a clinical history suggesting metal allergy may be pre-tested. Results can be used to establish the most compatible materials and metals for the implant. Second, MELISA can be used to confirm if metal hypersensitivity is contributing to any symptoms that develop post-surgery.

Metal allergy and orthopaedics

Metal allergy is a well-documented factor in the failure of implants [4]. The need for allergy testing in sensitive patients is recognized by both implant manufacturers [4] and by surgeons [5, 6] alike. The prevalence of metal hypersensitivity in patients with implants is significantly higher than in the general population, with an even higher prevalence rate among patients with failing implanted devices [5].

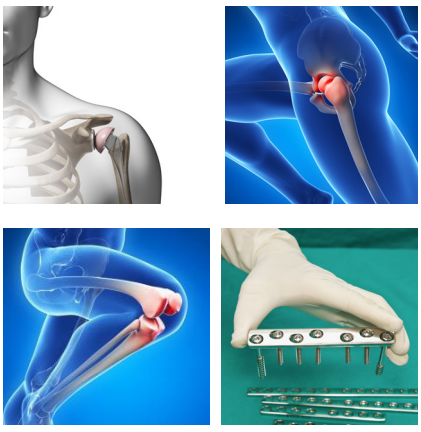


Data from Hallab et al 2001 [7]

To arrange testing:
call +44 20 8133 5166 or email julia@melisatest.com

MELISA testing

MELISA is an optimised 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 surgery, a panel of the 20 most commonly used metals is available. Testing for hypersensitivity to some of the constituents of cements and adhesives is also possible.
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.



MELISA testing versus 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 sensitised T cells [7] and the relationship between skin hypersensitivity and systemic hypersensitivity is ill defined [8, 9]. Lack of standardisation 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 detect any positive reactions to titanium in over a decade of patch testing [11], despite several cases of titanium allergy published by others [12, 13]. Traces of other metals such as nickel and aluminium are found even in commercially pure titanium due to the production process [14, 15]. Titanium has been shown to induce clinically relevant hypersensitivity which can be detected with MELISA testing [16].

Allergy and toxicity

Metal-on-metal implants are linked to raised levels of metal ions in the blood. When levels become excessively high, the ions are absorbed by the cells and can no longer be excreted from the body. This accumulation of metal ions may trigger an immune response.

All implant alloys release metal ions, but some metal-on-metal prostheses release many more ions than previously thought [17]. The ions can leak into the surrounding tissue and cause reactions that affect both bone and muscle and may leave patients with disabilities [18].

Instead of measuring levels of metal ions in a patient's body, MELISA measures how the patient's immune system reacts to specific metals. There are no generally accepted guidelines as to what constitutes an unacceptably high level of ions in blood for patients with orthopaedic implants [17]. As an example, the Medicines and Healthcare Products Regulatory Agency (MHRA) indicates patients with a threshold level of 7 µg/L of cobalt [19] in their blood should be investigated, although it is unclear how this figure was derived. In fact, studies show that blood cobalt concentrations generated through the wear of some of the newer metal-on-metal total hip prostheses can reach over 300 µg/L [17].

In MELISA, each antigen is tested in multiple concentrations to achieve the optimal result for each patient. A wide range of metals can be tested including less commonly tested elements such tantalum, niobium and manganese. Testing is also possible for some constituents of bone cements including methyl methacrylate (MMA).

Indicators for MELISA testing

- Ongoing pain or discomfort – particularly in the groin [20]
- Cutaneous metal hypersensitivity – dermatitis, urticaria, vasculitis [7]
- Fibromyalgia, chronic fatigue, autoimmune disease
- Raised blood metal ion levels
- Adverse local tissue responses (ALTRs) presenting as:
    - Pseudotumours
    - High ALVAL (aseptic lymphocyte-dominated vasculitis-associated lesion) score – including loss or necrosis of synovial lining, lymphocyte presence [21]
    - Osteolysis

Life threatening metal allergy treated through "immunological camouflage" of implant

This case report describes an innovative solution for patients with metal allergies needing implants. A young boy with syndromic scoliosis had metal rods implanted in his chest and developed severe post-operative symptoms. MELISA testing showed that the boy was allergic to several metals found in the implant. Symptoms resolved after the rods were removed. Eventually the rods were "camouflaged" from the patient's immune system by an innovative carbon coating and the boy was able to tolerate the implant.

Zielinski et al, 2014 [22]

Orthopaedic conference reports health improvement in metal allergic patients after revision

"Of the allergic patients who underwent revision surgery to change their implants and remove the allergen, 78% reported that they were "moderately" or "a lot" better."

Karin Pacheco, MD, Annual Meeting, American Academy of Orthopaedic Surgeons 2014 [23]

Implant alloys

It is recommended that the exact composition of an implant is established prior to testing. However, metals usually found in common medical grade alloys include:

Cobalt Chrome	Cobalt	Chromium	Molybdenum	Nickel
Stainless Steel	Chromium	Nickel	Molybdenum	Manganese
Titanium alloy I	Titanium	Vanadium	Aluminium	Nickel traces
Titanium alloy II	Titanium	Aluminium	Niobium	Tantalum

MELISA Diagnostics offers MELISA testing in the United Kingdom but is also looking for research partners to study allergy in patients with implants. In addition, we would like to work with specialists to develop allergy testing for all materials commonly used in implanted medical devices, such as metals, adhesives and cements.

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 tubes containing sodium citrate (light blue). 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.

Steroids or other immuno-suppressant drugs may affect the test results.

To help identify patients who are likely to benefit from MELISA testing, a questionnaire can be used. However, patient history alone is not sufficient to diagnose metal hypersensitivity [24].

References

1) Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007 Apr;89(4):780-5.
2) Pinson ML, Coop Ca, Webb CA. Metal hypersensitivity in total joint arthroplasty: Annals of Allergy, Asthma & Immunology In Press.
3) Valentine-Thon E, Schiwara HW. Validity of MELISA® for metal sensitivity testing. Neuroendocrinology Letters 2003;24(1/2):57-64.
4) Aesculap Implant systems brochure 2009 http://www.aesculapimplantsystems.com
5) Rushinga G, Goretsky M, Gustin T, Morales M, Kelly R, Nuss D. When it is not an infection: metal allergy after the Nuss procedure for repair of pectus excavatum. Journal of Pediatric Surgery 2007;42:93-97.
6) Adala R, Chakravarthy M, Srinivas V, Pai S. Orthopaedic surgery in a patient with metal sensitivity. J Cutan Aesthet Surg. 2011;4(1): 67-68.
7) Hallab, N. PhD, Merritt, K. PhD, Jacobs, J. Metal sensitivity in patients with orthopedic implants. The Journal of Bone and Joint Surgery 2001;83:428.
8) Cambell P; metalsensitivity.com.
9) 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.
10) Fischer LA, Johansen JD, Menné T. Methyldibromoglutaronitrile allergy: relationship between patch test and repeated open application test thresholds. Br J Dermatol. 2008 Nov;159(5):1138-43.
11) 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.
12) Thomas P, Bandl WD, Maier S, Summer B, Przybilla B. Hypersensitivity to titanium osteosynthesis with impaired fracture healing, eczema, and T-cell hyperresponsiveness in vitro: case report and review of the literature. Contact Dermatitis. 2006 Oct;55(4):199-202.
13) Evrard L, Waroquier D, Parent D. Allergies to dental metals. Titanium: a new allergen. Rev Med Brux. 2010; 31(1):44-9.
14) Schuh A, Thomas P, Kachler W, Goske J, Wagner L, Holzwarth U, Forst R. Allergic potential of titanium implants. Orthopade. 2005;34(4):327-8, 330-3.
15) Darvell, BW et al. Contamination of titanium castings by aluminium oxide blasting. J Dent. 1995 Oct;23(5):319-22
16) Müller K, Valentine-Thon E. Hypersensitivity to titanium: Clinical and laboratory evidence. Neuroendocrinology Letters Volume 27 Suppl. 1 2006; 27(Suppl 1):17–24.
17) Cohen D. How safe are metal-on-metal hip implants? BMJ 2012;344:e1410.
18) Grammatopolous G, Pandit H, Kwon YM, Gundle R, McLardy-Smith P, Beard DJ, et al. Hip resurfacings revised for inflammatory pseudotumour have a poor outcome. J Bone Joint Surg Br 2009;91:1019-24.
19) MHRA. Medical device alert: all metal [MoM] hip replacements. MHRA, 2010.
20) Campbell P, Shimmin A, et al. Metal sensitivity as a cause of groin pain in metal-on-metal hip resurfacing. J Arthroplasty. 2008;23(7):1080-5.
21) The Hip Resurfacing Handbook: A Practical Guide to the Use and Management of Modern Hip resurfacings edited by K De Smet, P. N. Woodhead Publishing 2013.
22) Zielinski J, Lacy TA, Phillips JH. Spine Deformity. 2014;2:76-80
23) American Academy of Orthopaedic Surgeons (AAOS) 2014 Annual Meeting: Abstract 120. Presented March 11, 2014.
24) 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.

MELISA Diagnostics Ltd
t +44 (0)20 8133 5166 f +44 (0)20 8711 5958 e info@melisatest.com w melisatest.com & melisa.org

MELISA® DIAGNOSTICS